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References: **1.** Pickering, D. E., and Lusted, L. B.: GP *11*:99 (Feb.) 1955. **2.** Perloff, W. H.: J.A.M.A. *157*:651 (Feb.) 1955. **3.** Watson, B. A.: New York State J. Med. *54*:2045 (July 15) 1954. **4.** Panos, T. C.: South. M. J. *48*:527 (May) 1955.

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EFFECT OF CORTICOTROPIN AND PREDNISONE ON THE EXCRETION OF ALDOSTERONE IN MAN*

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THE physiologic factors which regulate the secretion of aldosterone are still not clearly defined. That more than one mechanism may be involved is indicated by the studies of various investigators. The observations of Leutscher and Johnson (1) and Liddle *et al.* (2) show that changes in sodium metabolism influence aldosterone secretion, and those of Laragh and Stoerk (3), Singer and Stack-Dunne (4) and Leutscher and Curtis (5) support the view that potassium is also of importance in this respect. In addition, the possibility that volume changes in body-fluid compartments may affect aldosterone secretion is suggested by the studies of Beck *et al.* (6).

Conflicting findings have been reported on the influence of corticotropin (ACTH) on aldosterone secretion. Simpson and Tait (7) found that the administration of this hormone did not increase the concentration of aldosterone in the blood and several investigators (8–10) have failed to demonstrate any effect on the output aldosterone in the urine. In two other studies, however, it was found that corticotropin caused an increase in aldosterone excretion; one study was by Gordon *et al.* (11) in a patient with rheumatoid arthritis, and one by Liddle *et al.* (2) in a normal subject. Studies on hypophysectomized animals suggest that the anterior lobe of

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the pituitary may play some role in the regulation of aldosterone release. Singer and Stack-Dunne found that administration of corticotropin restored to normal the aldosterone content of the adrenal venous blood of hypophysectomized rats, and Farrell *et al.* (12) demonstrated that the rate of aldosterone secretion in hypophysectomized dogs remained at two-thirds of the normal amount. Luetscher and Axelrad (13) reported that patients with hypopituitarism have normal levels of aldosterone in the urine.

In the present study we have re-investigated the effect of administration of corticotropin on aldosterone excretion in normal subjects and in patients with rheumatoid arthritis and have measured the output of aldosterone in patients with hypopituitarism. We have also investigated the effect of prednisone on aldosterone excretion.

CHEMICAL METHODS

Aldosterone was assayed by means of a modified procedure of the Singer-Venning bioassay (14). The sodium-retaining hormone was extracted from the urine before and after hydrolysis at pH 1.5 for twenty-four hours. The fractions were combined and were purified by paper chromatography prior to assay. The corticoids were determined as 17,21-dihydroxy-20-ketosteroids by the method of Porter and Silber (15), and the 17-ketosteroids by the method of Callow *et al.* (16). Urinary sodium and potassium were measured by flame photometry. Cortisone was used as the standard in the Porter-Silber method.

CLINICAL MATERIAL

Three healthy young male physicians were selected for controls and were studied over periods ranging from eight to fourteen days. They carried out their usual activities in the hospital during the investigation and 24-hour collections of urine were made daily.

The effect of corticotropin on aldosterone excretion was determined in these 3 normal men and in 3 women with rheumatoid arthritis; the effect of prednisone was studied in 1 man with asthma and in 1 of the 3 women with rheumatoid arthritis. Aldosterone excretion was also determined in 9 patients with hypopituitarism.

Case Reports

Normal subjects

Case 1. R.M. was a healthy male, aged 28 years. Urine collections were begun on a day on which he wrote a three-hour examination paper. On the sixth, seventh and eighth

days he received 100 units of corticotropin (Acton-X[1]) intramuscularly daily in four doses. A marked retention of sodium and water ensued, causing edema of the feet and legs up to the knees and some swelling of the face, with a gain in weight of 12 pounds. There was also some epigastric discomfort. As may be seen in Figure 1, during the first five days the urinary corticoids ranged from 2.15 to 2.89 mg., and the 17-ketosteroids from 25.6 to 29.4 mg. per twenty-four hours. The administration of corticotropin (ACTH) resulted in an increase in the corticoid excretion to 10.0 mg., and in the 17-ketosteroid excretion to 126.8 mg. per twenty-four hours. The urinary sodium decreased to a level of 6 mEq. per twenty-four hours. On the first day of study, the aldosterone excretion was 8.7 μg. (above the normal range) and gradually decreased on the following

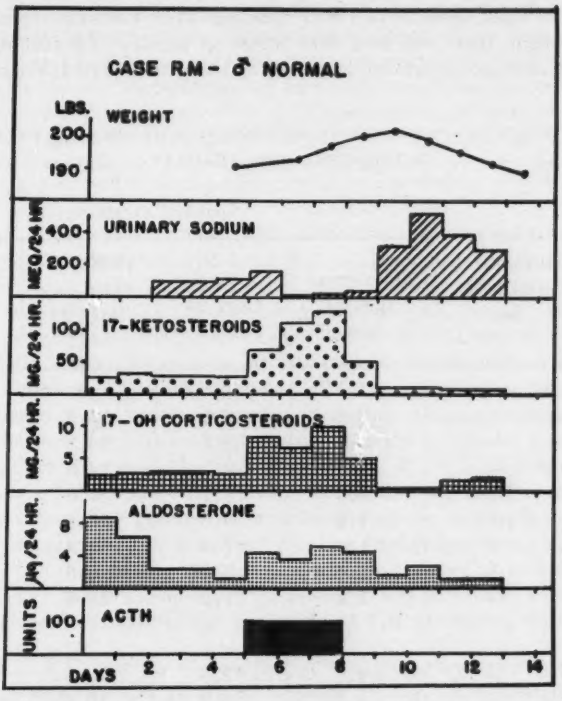

FIG. 1. Effect of corticotropin (ACTH) on aldosterone excretion in a healthy male. (Day 1—examination)

days to 1.3 μg. per twenty-four hours. With the administration of corticotropin, aldosterone excretion increased to 5.6 μg. per twenty-four hours. Following withdrawal of corticotropin the excretion of the various adrenocortical metabolites declined to levels below those observed in the control period.

Case 2. O.R. was a healthy male, aged 27 years. After a control period of three days,

[1] Acton-X was kindly supplied by Mr. K. Antoft of Nordic Biochemicals Limited.

he received 100 units of corticotropin (Acton-X) intramuscularly for two days. This was followed by water and sodium retention and a gain in weight. The urinary 17-ketosteroids increased from 25 mg. to 78.4 mg. per twenty-four hours and the corticoids from 2.3 mg. to 10.2 mg. per twenty-four hours. A slight increase in aldosterone excretion was observed during the administration of corticotropin; the values, however, did not exceed the normal range. When corticotropin was discontinued the excretion of these steroids decreased to levels below those observed in the control period. These results are shown in Table 1.

Case 3. J.B. was a healthy male, aged 31 years. After a control period of three days, he received 100 units daily of an aqueous preparation of corticotropin (Armour) intramuscularly in four equal doses for two days. Although there was some retention of water and a gain in weight, there was very little effect on urinary 17-ketosteroid excretion and only a small increase in corticoid excretion. In the control period, aldosterone excre-

TABLE 1. EFFECT OF CORTICOTROPIN ON EXCRETION OF ADRENAL METABOLITES IN 2 HEALTHY MALE SUBJECTS

Day	Dose of corticotropin (units/24 hrs.)	Urinary excretion			
		Aldosterone (μg./24 hrs.)	Corticoids (mg./24 hrs.)	17-Ketosteroids (mg./24 hrs.)	Sodium (mEq./24 hrs.)
Case 2. O.R.					
1	—	3.6	2.3	25.0	158
2	—	3.3	2.3	25.8	197
3	—	1.0	2.2	24.3	234
4	100*	4.3	10.2	37.6	65
5	100*	4.2	9.5	70.8	37
6	—	1.2	7.3	78.4	95
7	—	1.4	0.8	15.6	264
8	—	1.3	1.2	13.5	505
Case 3. J.B.					
1	—	4.6	2.3	13.1	—
2	—	4.8	3.2	10.6	—
3	—	9.2	4.2	12.0	—
4	100†	7.5	5.5	9.5	—
5	100†	2.8	5.9	9.5	—
6	—	13.5	1.4	6.3	—
7	—	2.7	4.5	8.2	—
8	—	1.9	3.1	8.0	—
9	—	0.8	3.6	8.4	—
10	—	3.0	4.3	9.4	—

* Acton-X—Nordic Biochemicals Limited.
† Armour's aqueous preparation.

tion varied; on the third day it was 9.2 μg. per twenty-four hours—a value above the normal range. These levels decreased on administration of corticotropin. On the day following the withdrawal of corticotropin, aldosterone excretion increased to 13.5 μg. per twenty-four hours. On subsequent days the amounts excreted were within the normal range. No urinary sodium determinations were made in this study. The results are shown in Table 1.

Rheumatoid arthritis

Case 4. W.W., a 21-year-old woman, had suffered from rheumatoid arthritis for six years; she had pain, swelling and limitation of movement in her hands and feet. On admission to the hospital, a metabolic balance study was started with a constant intake of protein, sodium and potassium. After a control period of five days, she received 80 units of corticotropin (Armour) daily (20 units intramuscularly every six hours) for five days. With this therapy the excretion of corticoids and 17-ketosteroids increased. The aldosterone output, which averaged 3.0 μg. per twenty-four hours in the control period, increased to 10.5 μg. on the sixth and seventh days. On the eighth and ninth days it had decreased to 6.3 μg. in spite of continued treatment with corticotropin. The results are shown in Table 2.

Case 5. J.B., a 51-year-old woman, had suffered from rheumatoid arthritis since 1937. Metabolic studies were started, with a constant intake of protein, sodium and potassium. The daily diet contained 86.9 mEq. of sodium and 102.5 mEq. of potassium. After a control period, she received 100 units of aqueous corticotropin (Armour) daily intramuscularly for five days and then the dosage was gradually reduced over a period of seven days to 40 units daily. At this stage, aqueous corticotropin was replaced with a long-acting preparation, Duracton. The initial daily dose of this preparation was 30 units, which was gradually reduced over a twelve-day period to 5 units. Aldosterone assays were carried out during the first ten days and subsequently on the twentieth, twenty-eighth and twenty-ninth days. The results are shown in Table 2. At the beginning of therapy with corticotropin, the aldosterone output in the urine was doubled. With continued treatment, however, the levels gradually decreased and on the twentieth day (after fifteen days of corticotropin therapy) less than 0.5 μg. per twenty-four hours could be detected in the urine. The corticoids at this time were being excreted at a rate of 10 mg. per twenty-four hours. When the dosage of corticotropin was reduced to 5 units, the urinary corticoids decreased and aldosterone increased to 1.8 μg. per twenty-four hours.

Case 6. M.T., a 57-year-old woman, had suffered from rheumatoid arthritis for seven years. She had been receiving 25 mg. of cortisone per day. On admission to the hospital all therapy was stopped. Metabolic balance studies were started, and the patient was maintained on a constant diet. The sodium and potassium intakes were 86.9 mEq. and 102.5 mEq. per twenty-four hours, respectively. After a control period of seven days, an aqueous preparation of corticotropin was administered intramuscularly for twelve days. The dose levels and results are shown in Figure 2. Therapy was omitted for seven days, and the patient was then given 30 mg. of prednisone (Meticorten, Schering) daily by mouth for fourteen days. This was followed by a second administration of corticotropin —in the form of long-acting Duracton; the initial dosage was 40 units, and this was gradually reduced to 5 units daily. During the first administration of corticotropin (aqueous), urinary corticoids increased from an average of 1.7 mg. to 9.5 mg. per twenty-four hours and remained at a relatively high level throughout the period of treatment.

TABLE 2. EFFECT OF CORTICOTROPIN ON EXCRETION OF ADRENAL METABOLITES IN 2 WOMEN WITH ARTHRITIS

Day	Dose of corticotropin (units/24 hrs.)	Urinary excretion			Urinary Na-K ratio
		Aldosterone (μg./24 hrs.)	Corticoids (mg./24 hrs.)	17-Ketosteroids (mg./24 hrs.)	
Case 4. W.W. (age 21 yrs.)					
1 & 2	—	2.3	1.6	0.8	1.16
3 & 4	—	3.8	0.8	1.1	0.77
5	80*	—	—	—	0.56
6 & 7	80*	10.5	8.4	3.7	0.64
8 & 9	80*	6.3	8.8	3.8	1.44
Case 5. J.B. (age 51 yrs.)					
1 & 2	—	1.4	2.8	—	0.94
3 & 4	—	3.8	2.7	—	0.67
5	—	3.6	2.8	—	0.67
6	100*	7.0	6.8	—	0.51
7 & 8	100*	5.6	9.2	—	0.68
9 & 10	100*	4.6	11.4	—	0.87
21	20†	<0.5	10.0	—	0.82
28 & 29	5†	1.8	3.5	—	0.72

* Armour's aqueous preparation.
† Duracton (long-acting).

During the control period sodium balance was positive, and during corticotropin therapy increased amounts of sodium were retained. On reduction of the dose and then withdrawal of corticotropin, the patient excreted increased amounts of fluid and sodium and there was a significant negative sodium balance. Aldosterone excretion in the control period varied between 1.0 and 4.8 μg. per twenty-four hours; coincident with the administration of corticotropin, it increased to 10.7 μg. per twenty-four hours. This level was maintained for three days. With continued administration of corticotropin, aldosterone excretion gradually decreased until it was less than 0.5 μg. per twenty-four hours. Following the period of negative sodium balance the aldosterone in the urine increased to 11.9 μg. per twenty-four hours for three days and at the same time the sodium balance became positive. Little change in the potassium excretion occurred. The sodium-potassium ratio in the urine decreased to 0.09 at the peak of aldosterone excretion. During the second administration of corticotropin (long-acting), the excretion of aldosterone again increased temporarily—to 10.1 μg. per twenty-four hours and then gradually decreased as corticotropin was continued. The administration of prednisone had no effect on the output of aldosterone.

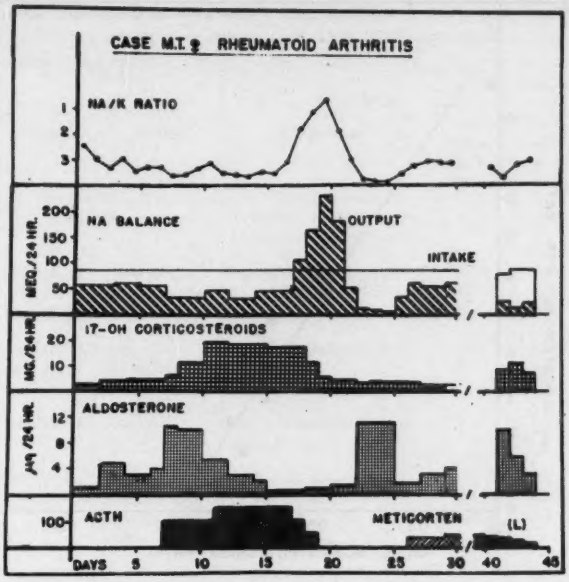

FIG. 2. Effect of corticotropin (ACTH) and prednisone (Meticorten) on aldosterone excretion in a woman with rheumatoid arthritis.

Asthma

Case 7. R.M. was a 31-year-old man who had suffered from intrinsic asthma since the age of 18 years. At the time of the study, emphysema and chronic sinusitis had developed. He was treated with prednisone and felt much better, although pulmonary function studies showed essentially no change from the original findings.

Urinary 17-ketosteroids, 17,21-dihydroxycorticosteroids and aldosterone were determined and the results are shown in Figure 3. The administration of 20 mg. daily of prednisone by mouth had little effect on urinary corticoids and aldosterone, but the 17-ketosteroids were depressed below the control level. The excretion of aldosterone was within normal limits, ranging from 2.4 to 5.7 μg. per twenty-four hours.

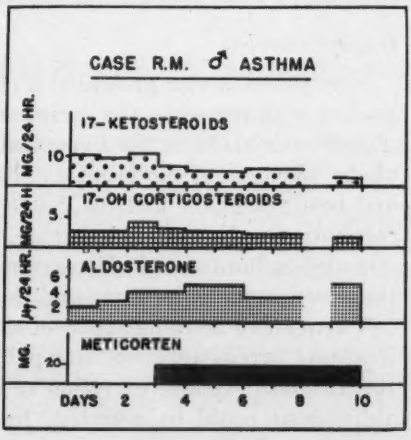

FIG. 3. Effect of prednisone (Meticorten) on aldosterone excretion in a male patient with asthma.

The aldosterone output of the 3 patients with rheumatoid arthritis was plotted against the logarithm of the sodium-to-potassium ratio in the urine (Fig. 4). An inverse relation-

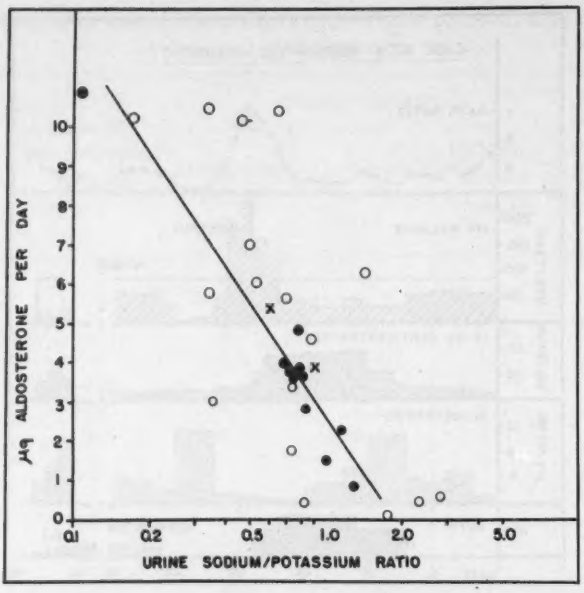

FIG. 4. Urinary sodium-to-potassium ratios (log scale) and aldosterone excretion. The solid circles represent the days with no therapy, the crosses represent prednisone therapy, and the open circles corticotropin therapy.

ship existed between the sodium-potassium ratio and the aldosterone excretion on the days when no therapy was given. When corticotropin was administered this relationship did not always hold.

Hypopituitarism

Nine patients who presented a clinical picture of hypopituitarism were studied with regard to the excretion of aldosterone. Four had been hypophysectomized. In 8, the hypopituitarism had been caused by a chromophobe adenoma of the pituitary. In 1 (hypophysectomized) the diagnosis had been malignant meloma. Some were being maintained on cortisone or corticotropin. Urinary aldosterone, corticoids, 17-ketosteroids and follicle-stimulating hormone (FSH) were measured. The results of the assays and the description of the cases and therapy are listed in Table 3.

Twenty-two determinations of aldosterone excretion were made in these 9 cases of hypopituitarism. In 6 patients in whom studies were made before therapy was started, excretion of aldosterone was normal in 5; in 1 no aldosterone could be detected. In each of the 4 receiving cortisone the excretion of aldosterone upon one determination was zero; but in 2 of

TABLE 3. URINARY ALDOSTERONE IN 9 PATIENTS WITH HYPOPITUITARISM: EFFECT OF CORTISONE AND CORTICOTROPIN

Patient	Age and Sex	Date	Therapy	Clinical status	Urinary excretion			
					Aldosterone (μg./24 hrs.)	Corticoids (mg./24 hrs.)	17-Ketosteroids (mg./24 hrs.)	FSH (m.u./24 hrs.)
D.A.	30 M	June 28, '54	25 mg. cortisone	Twenty-six days after hypophysectomy. Malignant meloma.	0	1.9	1.0	−6.6
D.T.	47 M	Nov. 17, '54	7 units duracton	Panhypopituitarism (16 yrs.)	0	0.36	0.7	−6.6
		Nov. 24, '54	5 units duracton		<1	0.35	0.5	
		Mar. 23, '55	5 units duracton		0	0.10	0.1	
W.R.	64 M	June 17, '55	None	Panhypopituitarism (2 yrs.)	4.2	0.17	1.6	−6.6
		Sept. 21, '55	37.5 mg. cortisone +testosterone		0	0.1	5.6	
H.L.	60 M	June 23, '55	None	Twenty years after hypophysectomy.	1.9	0.48	6.6	+13.2
A.L.	49 M	July 16, '55	None	Panhypopituitarism; 11 yrs. after hypophysectomy.	—	0.2	0.7	−6.6
			75 mg. cortisone		0–3.0	6.4	6.4	
			80 units corticotropin		0–2.7	18.0	14.8	
R.M.	61 F	June 13, '55	None	Moderate hypopituitarism; 7 days after hypophysectomy.	0	2.4	5.3	+105
		June 23, '55	50 mg. cortisone		0	5.8	2.8	
		June 25, '55	37.5 mg. cortisone		1.9	3.0	3.7	
M.B.	21 F	June 9, '55	None	Mild hypopituitarism	1.4	2.3	8.7	+13
		June 11, '55	None		2.5	2.3	9.6	
S.W.	18 F	Nov. 8, '55	None	Hypopituitarism, 8 months.	6.5	1.0	2.5	−6.6
D.M.	52 F	Nov. 4, '55	None	Panhypopituitarism following x-ray therapy of pit. tumor 8 years before.	6.6	1.4	0.1	−6.6
		Nov. 11, '55	80 units corticotropin		4.0	2.2	1.4	

these, values of 3.0 μg. per twenty-four hours were obtained upon other occasions.

D.T., a man who had had panhypopituitarism for sixteen years, was maintained on 5–7 units of long-acting corticotropin. In spite of this, the urinary corticoids and 17-ketosteroids were markedly decreased and no aldosterone could be detected.

A.L. was a 49-year-old man with panhypopituitarism. Figure 5 shows the results of a study of the effect of corticotropin on the excretion of adrenal metabolites. A chromophobe adenoma had been removed in 1944; in 1953, the patient was re-operated upon for recurrence of the tumor. Prior to treatment urinary 17-hydroxycorticosteroids were 0.2 mg., and 17-ketosteroids 0.7 mg per twenty-four hours. The FSH titer was negative at 6.6 mouse units per twenty-four hours. The initial medication consisted of a daily dose of 75 mg. of cortisone. Then corticotropin was added—first as 80 units daily of aqueous preparations (Armour's for five days, and Nordic Biochemicals' for ten days), and then 5 units daily of long-acting preparation (Duracton). During cortisone therapy, the excretion of aldosterone was on one occasion zero and on another 3.0 μg. per twenty-four

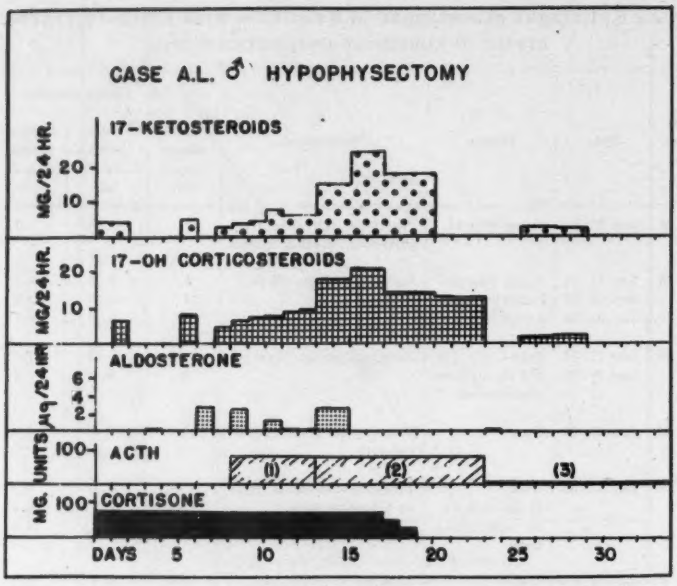

FIG. 5. Aldosterone excretion in a male patient with panhypopituitarism.

hours. With the administration of the first preparation of corticotropin there was a progressive decline in the output of this hormone. When the second preparation of corticotropin was administered, there was a greater increase in corticoid and 17-ketosteroid excretion, and aldosterone was again present in the urine. However, after ten days of this therapy no aldosterone could be detected.

DISCUSSION

The results of these various studies indicate that corticotropin plays only a minor role in the release of aldosterone. In 2 healthy young men administration of corticotropin caused only a slight increase in the excretion of aldosterone and the levels reached were within the limits of daily variations observed in normal subjects (*i.e.*, 1.0–6.3 μg. of aldosterone per day). On withdrawal of corticotropin, aldosterone excretion returned to lower levels and no change was observed during the diuresis that followed. In another healthy young man (J.B., Case 3) administration of corticotropin resulted in a decreased output of aldosterone. As there was also a lowering of urinary 17-ketosteroids and only a slight increase in 17-hydroxycorticosteroids, the potency of the preparation was questioned. It was found, however, to be active in other patients, and in J.B. it caused water retention as indicated by a gain in weight of 5 pounds. On withdrawal of corticotropin, and coincident with the diuresis that followed, the aldosterone excretion increased significantly. The wide variations in

excretion of this hormone observed in this subject preclude any interpretation of the findings. The level of aldosterone excretion was above the normal range prior to administration of corticotropin.

As only a small portion of the total amount of urinary aldosterone is present as free steroid, the failure in earlier studies to observe changes in aldosterone excretion in healthy subjects following administration of corticotropin may have been partly due to the fact that unhydrolyzed urine was used in these experiments. As these extracts were not purified by chromatography prior to assay, it is possible that other substances were present in the crude fraction which might have interfered with the bioassay of aldosterone.

In all 3 women patients with rheumatoid arthritis there was a normal output of aldosterone and it was possible to demonstrate an immediate increase in the excretion of this hormone with the beginning of corticotropin therapy. In 2 of these patients, the levels reached were well above the normal range. As treatment with corticotropin was continued, the amount of aldosterone in the urine gradually decreased and in 1 case, after nine days of therapy, aldosterone was not detectable. The loss of sodium and water which occurred after withdrawal of corticotropin appeared to be a stimulus for the elaboration of increased amounts of aldosterone in 1 of these patients. A similar effect was observed in 1 of the normal men. Luetscher *et al.* (17) also found that in some patients with nephrosis the sodium-retaining hormone may be increased when corticotropin is first administered, but is decreased when diuresis occurs.

These studies suggest that, with regard to aldosterone excretion, patients with rheumatoid arthritis may exhibit an initial greater response to corticotropin stimulation than do normal subjects. However, the cases studied are too small in number to permit conclusions to be drawn.

In the 2 studies with prednisone, the administration of this hormone had little effect on the excretion of aldosterone. In both patients the output of aldosterone was within normal limits. Liddle *et al.* (2) have administered cortisone to normal subjects without effect on aldosterone excretion (as in patients with nephrosis). Luetscher and Deming (18) found that, when urinary aldosterone is elevated, cortisone administration frequently initiates a diuresis which is accompanied by a reduction in aldosterone excretion. These findings were confirmed by McCall and Singer (19). It has been shown by Luetscher and Curtis (5) that the ratio of potassium to sodium in the urine in healthy subjects on different intakes of sodium inversely reflects the amount of aldosterone excreted, and Garcia-Llaurado (20) has reported a correlation between aldosterone activity and the urinary sodium-to-potassium ratio in patients under surgical stress. In the present study a reverse relationship of sodium-to-potassium ratio and

aldosterone output was observed in patients with rheumatoid arthritis on a constant electrolyte intake. When corticotropin was administered, however, many of the ratios failed to show a correlation with aldosterone excretion. Under these conditions there is a greatly increased output of corticosteroids, which may also affect the electrolyte balance. Thus, other factors besides aldosterone may influence this ratio.

The results in the patients with hypopituitarism agree with the findings of Luetscher that these subjects may excrete normal amounts of aldosterone. The administration of cortisone and of corticotropin resulted in some decrease in the excretion of aldosterone; and in several instances, no aldosterone could be detected in the urine.

SUMMARY

The administration of corticotropin caused a slight increase in aldosterone excretion in 2 of 3 healthy young men.

The administration of corticotropin to 3 women with rheumatoid arthritis caused a significant temporary increase in aldosterone excretion. As therapy with this hormone was continued, aldosterone excretion decreased to low levels. On withdrawal of corticotropin, there was a diuresis with loss of sodium; following this, there was a significant increase in urinary aldosterone. When no medication was being administered, there was an inverse correlation between the sodium-potassium ratio and aldosterone excretion in the urine of these patients.

The administration of prednisone did not appear to have any effect on the excretion of aldosterone in 1 patient with asthma and in 1 of the 3 patients with rhuematoid arthritis.

Aldosterone was excreted in normal amounts in 5 of 6 patients with hypopituitarism. In 4 who were being treated with cortisone, no urinary aldosterone could be detected. Corticotropin appeared to have very little effect on the excretion of aldosterone in these patients.

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STUDIES ON AN IODINATED PROTEIN IN THE SERUM OF SUBJECTS WITH CANCER OF THE THYROID*†

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TUMORS of endocrine glands may possess functional activity and secrete "normal" hormones or substances with similar physiologic activity but different in chemical structure. Cancers of the thyroid in the absence of any normal tissue may maintain a subject in an euthyroid state. It has been demonstrated that some cancers of the thyroid, especially the metastatic variety, secrete thyroxine and triiodothyronine (1). Moreover, an iodinated substance, presumably protein in nature and not present normally, has been found in the blood of some patients with cancer of the thyroid (1). This material was shown to have an electrophoretic mobility at both pH 8.6 and pH 4.5 similar to that of serum albumin. It was not dialyzable and has a sedimentation constant $S_{20,w} = 4.2$ (2). This substance, designated compound X, could be hydrolyzed by trypsin or alkali and yielded monoiodotyrosine and a very small amount of thyroxine.

The present study was undertaken to investigate in more detail some of the properties of compound X labeled with I^{131} and, in particular, to evaluate its relationship to serum albumin.

METHODS AND RESULTS

I. *Subjects*

Three patients with thyroid cancer were chosen because their sera following the administration of I^{131} contained compound X in sufficient amount to permit detailed studies

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TABLE 1. CLINICAL AND LABORATORY DATA ON SUBJECTS

Patient	Age	Sex	Pathologic diagnosis (thyroid)	Functional tissue		Serum PBI (μg./100 ml.)	Dose of I^{131} (mc)	Per cent dose excreted in urine in 48 hrs.
				Normal thyroid	Thyroid carcinoma			
K.M.-I*	24	M	Papillary and follicular carcinoma	+	+(in nodes)	5.8	90	52.0
K.M.-II	24	M	Papillary & follicular carcinoma	Scant	+	2.2	250	68.2
M.G.-I	43	F	Papillary & follicular carcinoma	+	+	7.6	50	57.0
E.P.-I	39	F	Adenocarcinoma	Scant	+(mainly in lungs)	10.0	175†	—
E.P.-II	39	F	Adenocarcinoma	—	+	9.3	325†	—

* I and II represent the serial order in which the I^{131} was administered.

† These figures do not represent a single dose but indicate the total amount of I^{131} received up to the time of study; the patient received doses varying from 50 to 75 millicuries about every six weeks.

of this material. All[1] I^{131} was given orally in the form of NaI^{131}. Pertinent laboratory and clinical data[2] are included in Table. 1.

II. *Preliminary Analysis of Serum*[3]

Samples containing 10–50 ml. of serum were usually obtained between twenty-four and one hundred and forty-four hours after the administration of therapeutic doses of radioiodine. The radioactivity in the serum samples was measured in a well-type scintillation counter before using 5–10 microliters (μl.) of each sample for a chromatographic analysis on paper (Whatman No. 1, ascending). The following solvent systems were employed according to techniques of Roche *et al.* described elsewhere (3):

a) N-butanol-acetic acid-water (78:10:12, v/v).
b) N-butanol-dioxane (80:20, v/v) saturated with 2N NH_4OH.
c) Col'idine[4]-water (100:35.5, v/v); atmosphere of NH_3.
d) A fourth system made of ethanol-water (42.5–57.5, v/v) without buffering was found especially useful in distinguishing thyroglobulin in the presence of compound X, thyroxine, triiodothyronine and iodine. Thyroglobulin was immobile, but the other serum iodine compounds yielded Rf values between 0.60–0.75.

Control carrier amounts (15–25 micrograms (μg.)) of monoiodotyrosine, diiodotyrosine, thyroxine and triiodothyronine, and 5 μg. of potassium iodide were added to each chroma-

[1] All I^{131} used was obtained from Oak Ridge National Laboratories, Oak Ridge, Tennessee.

[2] We are indebted to Dr. Kenneth Corrigan, Harper Hospital, Detroit, for the serum from Patient E. P.

[3] The following abbreviations have been used throughout the text: I^- = Iodide. MIT = Monoiodotyrosine. DIT = Diiodotyrosine. HSA = Human Serum Albumin. T_4 = Thyroxine. T_3 = Triiodothyronine.

[4] The collidine was obtained from Eastman Organic Chemicals, and the fraction distilling over at 168°–170° was used.

togram strip before development. The amino acids were stained with 0.2 per cent Ninhydrin, and I^- by 0.7 per cent $PdCl_2$. The distribution of radioactivity on the paper chromatogram was recorded, as previously described (1), by running the strip through an automatic recorder.

Each serum sample was also analyzed by zone electrophoresis on paper (Whatman No. 3) in barbital buffer at pH 8.6 and $\Gamma/2 = 0.1$ (4). After drying, the distribution of the radioactivity was recorded and the strips were stained with bromphenol blue. In Table 2 are listed the data obtained on the distribution of I^{131} in different serum fractions analyzed by the foregoing methods.

Values lower than 1.0 per cent were not included in the calculations, since the error in measurement of areas is excessive at this level. The values in the column "Origin I^{131}" represent the fraction of total serum I^{131} that was immobile in chromatograms developed with the collidine and the two butanol systems. This fraction has been demonstrated to be made up of protein I^{131} in the form of serum thyroglobulin and compound X (1, 8).

TABLE 2. ANALYSIS OF SERUM I^{131}

Patient	Time after I^{131} dose (hrs.)	Total serum I^{131} (% dose/ml. $\times 10^{-3}$)	Chromatography*: % I^{131} in different fractions				Electrophoresis†: % organic I^{131} in protein fractions		
			Origin I^{131}	T_4	T_3	I^-	Albumin	$\alpha_1 - \alpha_2$ globulins	γ-globulins
K.M.-I	24	0.50	54.5	—	—	43.5	80.9	15.4	2.0
	48	0.39	90.7	1.2	—	9.1	82.2	11.7	4.6
	96	0.46	87.7	7.6	—	4.7	77.3	16.0	5.7
	144	0.62	84.4	10.5	—	4.4	70.6	28.0	1.4
K.M.-II	24	0.98	13.4	—	—	85.3	55.3	40.0	3.0
	48	0.40	30.6	18.2	2.6	48.5	48.6	47.3	3.6
	96	0.31	55.7	20.6	2.1	17.6	51.9	46.5	1.2
	144	0.30	62.5	29.1	1.6	8.6	52.8	43.4	2.0
M.G.-I	24	0.67	10.6	1.5	—	87.2	41.1	56.9	3.3
	48	0.29	29.2	1.8	—	66.8	30.7	61.6	6.5
	96	0.53	65.3	9.7	2.1	20.0	26.4	71.5	2.0
E.P.-I	24	—	59.2	9.6	—	31.1	93.2	6.1	—
	48	—	80.2	6.8	1.0	10.2	76.3	19.2	3.0
E.P.-II	24	—	67.1	7.1	—	23.8	88.5	9.5	2.0
	48	—	73.6	10.4	—	13.6	83.9	12.1	3.5

* Average values, using *n*-butanol/acetic acid/H_2O, and *n*-butanol/dioxane/NH_3 systems.
† Iodide not detected by electrophoresis, and values uncorrected.

Chromatograms developed in the ethanol-water system permit quantitation of the amount of thyroglobulin I^{131}, and in samples K.M-II, E.P.-I and E.P.-II this was found to be less than 20–25 per cent of the total I^{131} for the first forty-eight hours. These samples were therefore most suitable for a quantitative separation of compound X. In the electrophoretic analyses, the I^{131} distributed in the albumin fraction was considered to be in the form of compound X, although a small amount of thyroxine and triiodothyronine may also be bound to this protein. Most of the thyroxine, triiodothyronine and all the serum thyroglobulin are found in the position occupied by alpha-1 and alpha-2 globulins, in the manner previously described (1, 4).

III. *The Isolation of Compound X and Serum Thyroglobulin*

In the first experiments, the albumin fraction was obtained from the serum by precipitation with 1.75 M phosphate buffer to remove the serum thyroglobulin (1). The supernatant liquid, after removal of I^- by dialysis, was lyophilized to yield albumin and contaminating proteins plus compound X.

Two other methods were developed for the separation of serum albumin and compound X from other proteins. One is applicable to small amounts of serum and the other for larger-scale preparation.

a) *Electrophoretic separation*

A sample of serum (between 3 and 4 ml.) was deposited on a starch block and the electrophoretic separation carried out under 400 V. at +4° C. for about twenty-four hours according to the method described by Kunkel (5). An imprint of the starch block was made on a sheet of Whatman No. 1 filter paper which, upon staining with bromphenol blue reagent, revealed the positions of the different protein fractions. The section on the starch block corresponding to the position of serum albumin was cut out and eluted four times with 0.15 M NaCl solution until less than 5 per cent of its total radioactivity remained in starch. The eluate was dialyzed against water at +4° C. for twenty-four hours and then lyophilized. Chromatography and electrophoretic analysis of the product obtained showed a single peak of radioactivity in the albumin position. There appeared to be less than 10 per cent contamination with thyroxine or iodide, as determined by the foregoing methods of analysis.

b) *Chemical fractionation of serum proteins*

For the fractionation of several samples of serum, method No. 10 of Cohn *et al.* (6) was employed with some modifications. The volume of serum used varied between 5 ml. and 30 ml. All the procedures were carried out at a temperature of −5° C. and the protein precipitates were separated by filtration through a sintered glass filter cup with a maximum porosity of 14 microns under reduced pressure, as described by Lever *et al.* (7). In the preliminary studies, the precipitate and supernatant liquid obtained at each step was analyzed for the distribution of I^{131} compounds by chromatography and electrophoresis. The serum used for this procedure was known to contain easily detectable amounts of endogenously labeled triiodothyronine, thyroxine, thyroglobulin, compound X and iodide.

The first step led to the precipitation of "Fractions I+II+III," consisting mainly of gamma-globulins and beta-lipoproteins and all of the serum thyroglobulin (pH = 5.8, $\Gamma/2 = 0.04$; final concentration of Na = 0.04 M; final concentration of ethanol = 19 per cent). The supernatant liquid and the washings from this step were used for the second step, which involves the precipitation of "Fractions IV and V" at pH 5.8, in 19 per cent ethanol in the presence of 0.02 M zinc acetate. This fraction contains the serum albumin, all the I^{131} in the form of compound X, and a small amount of the thyroxine originally present. The use of barium to dissolve albumin as employed by Cohn *et al.* (6) was not found useful for our purposes, as this step neither separated compound X from the albumin nor did it remove the traces of contaminating thyroxine. On the other hand, when the precipitate from the second step was redissolved in 0.15 M NaCl, dialyzed at

+4° C. against water for twenty-four hours, and the non-dialyzable material again treated with 19 per cent ethanol and 0.02 M zinc acetate, most of the contaminating thyroxine disappeared. The final precipitate was redissolved, dialyzed against water and lyophilized. Analysis showed that from 90 to 96 per cent of the radioactivity in this fraction was compound X. This dry material represented the starting material for most of the studies on the nature of compound X.

When serum thyroglobulin was to be studied, the gamma-globulin precipitate from the first step was used after it was dissolved in 0.15 M NaCl, dialyzed against water at +4° C. for twenty-four hours and lyophilized. Analysis showed that about 90 to 96 per cent of the I^{131} in this protein fraction was in the form of thyroglobulin, as seen by "salting out," chromatographic and electrophoretic studies.

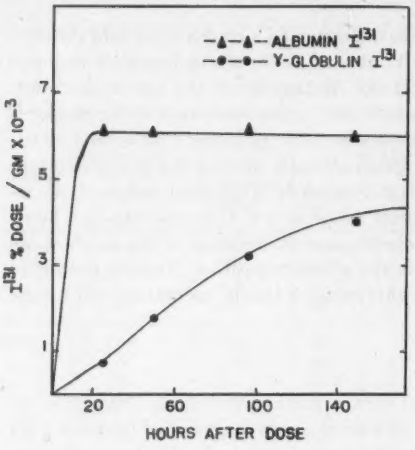

FIG. 1. Distribution of I^{131} in the two protein fractions of serum at different intervals during one week after radioiodine administration. The I^{131} in albumin represents that amount incorporated in compound X; and the I^{131} in gamma-globulin represents the appearance of labeled thryoglobulin in the serum. (Patient K.M.-II, in whom there was both normal and carcinomatous functioning thyroid tissue.)

Figure 1 shows the I^{131} content of the albumin fraction which consisted, from a radioactive standpoint, almost exclusively of compound X; the gamma-globulin fraction consisted of thyroglobulin. This figure represents data from a typical patient (K.M.-II) and shows the rapid appearance and early plateau of compound X and the slower rise and plateau of thyroglobulin in serum.

The level of serum thyroglobulin following large doses of I^{131}, as previously observed (8), increases rather slowly and does not reach the maximum until more than six days after the administration of I^{131}. The concentration of radioactive compound X was maximal twenty-four hours after the I^{131} was given. Any direct conclusion is difficult to draw from this phenomenon and its interpretation will be discussed later.

IV. *Sedimentation of Compound X in the Ultracentrifuge*[5]

The techniques and calculations for determining the sedimentation constant of compound X were the same as described by Petermann, Robbins and Hamilton (2). The

results on a typical albumin fraction of serum sample K.M.-II taken ninety-six hours after the administration of I^{131} are reported here. A 1 per cent solution of the serum albumin in 0.2 M NaCl was used, and the centrifugation was carried out at a speed of 52,640 r.p.m. in a Spinco ultracentrifuge with a standard 12-mm., 4° partition cell. In the case of the S values, corrections were applied for the amount of I^{131} in the thyroxine and I^- which were also present. The percentile distribution of I^{131} in the three iodine components of the albumin sample was calculated from the electrophoretic and chromatographic data. In this particular sample the distribution was: compound X, 94 per cent; thyroxine, 4 per cent; and I^-, 2 per cent.

The average value obtained from a series of five determinations for the sedimentation constant was 4.2 S at 20° C. and in 0.2 M NaCl. Using the partial specific volume for human serum albumin as equal to 0.73, a value of $S_{20,w} = 4.3$ was then obtained. These figures compare well with that of 4.2 S obtained by Robbins *et al.* (1, 2) on whole serum of a patient with thyroid cancer who was treated with I^{131}.

V. *Association of Compound X and Serum Albumin*

Chromatographic, chemical and electrophoretic analyses of all the albumin fractions prepared showed that the radioactivity from compound X was always associated with albumin. In the ultracentrifuge the $S_{20,w}$ value of 4.3 for compound X is very close to the value of 4.17 S obtained by optical methods for human serum albumin (HSA). Hence, compound X could represent 1 of at least 3 possible substances: 1) A complex of one or more iodinated compounds of small molecular weight very firmly bound to albumin; 2) an iodinated albumin; and 3) a substance containing iodine but distinct from albumin although resembling it in certain properties.

In preliminary studies, advantage was taken of some of the well known properties of solubility and complex-formation of human serum albumin, with a hope of dissociating it from the radioactive component. The effect of increasing concentrations of ethanol, methanol, acetone, ammonium sulfate, and a phosphate-buffer system (9) was studied on all the fractions of albumin in solution in 0.15 M NaCl. In all cases, the radioactivity followed the albumin, *i.e.*, the specific activity of albumin remained constant. Precipitation was also carried out by using salts of Hg^{++} and Zn^{++} but this again failed to separate the albumin from the I^{131} component. Extractions of an aqueous solution of albumin-compound X complex by organic solvents that are immiscible with water were carried out

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[5] This part of the work was carried out with Mrs. M. G. Hamilton at the laboratory of Dr. M. L. Petermann, Sloan-Kettering Institute. The authors wish to express their gratitude for advice and suggestions concerning the determination of the sedimentation constant values.

at different H^+-ion concentrations. The solvents used were: *n*-butanol, ether, chloroform, ethyl acetate and pyridine. The distribution of I^{131} in the aqueous and organic phase was less "clear-cut" than with the methods employing precipitation, but none of the organic solvents contained more than 15 to 25 per cent of the total radioactivity.

The failure of common methods based on solubility of albumin to separate the radioactive component from the protein led to the use of methods involving very specific properties of serum albumin. Two reactions that were applied successfully to achieve this separation and which indicated the nature of albumin-compound X association are as follows:

A. *Precipitin reaction on serum albumin-compound X*

The general principles of the precipitin reaction as described by Kabat and Mayer (10) were followed throughout, except for the modifications indicated. Instead of using nitrogen determinations, the precipitin curves were drawn from I^{131} determinations made on the precipitate and supernatant liquid. To determine whether compound X was an iodinated albumin, samples of I^{131}-tagged HSA, prepared by iodination with 0.5 to 4.0 atoms I/mole HSA, were used for the precipitin reaction for comparison with the albumin-compound X complex.

Preparation of I^{131}-labeled albumin: To a solution of 1 Gm. of HSA (Cohn Fraction V) in 7.2 ml. of a Na_2CO_3-$NaHCO_3$ buffer at pH 9.4 were added 3 ml. of 0.2 M KI containing 3.6 mg. of I_2 and 1 millicurie of carrier-free I^{131}. A subsequent addition of 1 M Na_2CO_3 was made to raise the pH to 10.1 and the solution left at +2° C. for twenty-four hours before dialysis against distilled water. The specific activity of the protein varied from 0.35 to 0.40 μc./mg. and its purity was checked for any other labeled iodo-compound by chromatography and electrophoresis. The amount of iodine fixed on the protein by this procedure was about 0.7 atom I/mole of HSA, and between 95 and 98 per cent of I^{131} was identified with the albumin.

Preparation of anti-albumin serum: Rabbits were sensitized to HSA (50–100 mg. per animal) according to techniques described by Freund and Bonanto (11) using adjuvants. A part of the serum was fractionated by ethanol according to the method described by Deutsch to obtain the gamma-globulin fraction containing the antibodies (12). This fraction was useful for the precipitin reaction on a preparative scale. For most purposes, the whole antiserum was used.

The following procedure was carried out for the precipitin reaction on samples of albumin-compound X and I^{131}-labeled HSA: 0.5 ml. of the anti-HSA serum was mixed with 0.5-ml. samples containing 25 micrograms to 5.0 milligrams of the protein. Sixteen dilutions were used for each curve. The antigen-antibody mixtures were left for three hours at 37° C. and then overnight at 4° C. before centrifugation. The precipitates were washed twice with 1.0 ml. of 0.15 M NaCl, and I^{131} measurements were made on the combined supernatant liquid and washing and on the precipitate dissolved in 0.1 M NaOH. Control experiments were also run on unlabeled HSA, in which the amount of protein in the precipitates was measured by ultraviolet absorption spectroscopy (at 275 mμ; Beckman, Model D-U). In Figure 2 are shown curves for the distribution of I^{131} with the albumin samples containing compound X and the I^{131}-albumin.

The distribution of radioactivity in the precipitates and the super-

natant portions for I^{131}-labeled HSA, as seen in Figure 2, follows the pattern usually seen for albumin in the precipitin reaction. The curve obtained for the unchanged native HSA measured by ultraviolet absorption spectroscopy was identical with that for I^{131}-labelled HSA, showing that the labeled protein preparation retained its immunologic reactivity (13). In the case of the albumin fraction obtained from the serum of the

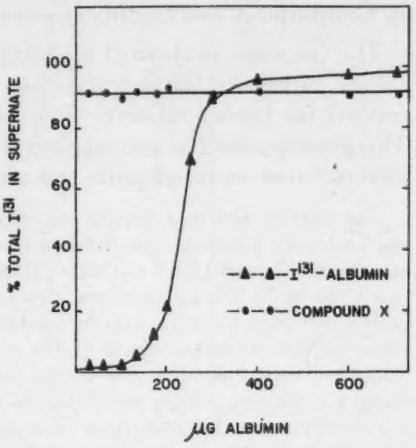

FIG. 2. Difference in distribution of I^{131} in a precipitin reaction with serum albumin containing labeled compound X and I^{131}-tagged HSA. Both reactions carried out under identical conditions and with the same anti-HSA rabbit anti-serum. The I^{131} curve obtained with iodo-albumin is similar to the one with untagged HSA as measured by ultraviolet spectroscopy.

subjects studied, the I^{131} accompanying the protein was distributed in a manner completely different than that of the I^{131} from the tagged iodo-albumin. Irrespective of the concentration of the antigen, the radioactivity was always found in the supernatant portions after the precipitation had taken place. At low concentrations of albumin there remained an excess of antibody in the supernatant liquid. This observation indicates that compound X represents neither an iodo-albumin nor an iodine compound physically bound to albumin (assuming that binding does not alter the immunologic behavior of albumin)—a situation similar to that observed in the binding of thyroxine and triiodothyronine to serum proteins.

A small sample of compound X, free of albumin, was prepared by this method as follows: a 20-ml. sample of a 5 per cent solution of HSA containing compound X (solutions made in 0.15 M NaCl) was mixed with a 0.5 per cent solution of gamma-globulins obtained from anti-HSA-rabbit serum. The amounts were adjusted so that an excess of gamma-globulin remained in the supernatant portion after the precipitation was complete. The supernatant fraction was then treated with ethanol, in a concentration sufficient to remove the excess of gamma-globulin while leaving any albumin that might be still in solution. Measurements by ultraviolet absorption spectroscopy showed that all the albumin was precipitated, although the final supernatant liquid retained from

90 to 95 per cent of the radioactivity. This latter fraction, upon chromatographic analysis using the two butanol systems and the collidine system, demonstrated a single immobile I^{131} peak, indicating that no iodinated amino acids were present. With the ethanol system chromatography and zone electrophoresis at pH 8.6, an irregular smear of radioactivity was found on the paper strip; the major part ended in the region that would have been normally occupied by albumin. This result is typical of adsorption on paper when unduly small amounts of proteins are used.

B. *Compound X and binding of sodium caprylate to serum albumin*

The increase in thermal stability of serum albumin when fatty-acid anions, especially the caprylate ion, are bound to it (14) has provided a method for freeing albumin from small amounts of other proteins (15). This phenomenon has been applied in the following studies on the nature of association of serum albumin and compound X.

The methods and experimental conditions have been described elsewhere by Teresi and Luck (14). Solutions of the different albumin fractions from the subjects under study and also of I^{131}-tagged HSA and native HSA were prepared in a 5 per cent concentration in 0.15 M NaCl. The solutions were divided into two equal parts. To one series of the protein solutions, a sodium caprylate solution was added, so as to have a final concentration of 0.02 M sodium caprylate. The other series served as a control. All the samples were then heated at 65° C. for twenty-four hours, and the precipitates collected. In samples containing sodium caprylate, the precipitate was not as dense and copious as in the other series. The separation was made by centrifuging at 15,000 r.p.m. for thirty minutes. Radioactivity measurements for I^{131} were made on the precipitates and the supernatant portions. In the case of untagged HSA the percentage of total protein remaining in the supernatant liquid was read by means of ultraviolet absorption spectrometry. The results of this experiment are listed in Table 3.

The distribution of I^{131} in samples of I^{131}-tagged albumin showed that the presence of sodium caprylate prevented its precipitation. Ultraviolet absorption measurements on native HSA samples similarly indicated that iodination of albumin with 1 atom of I/mole albumin did not impair the caprylate protection. On comparing the distribution of I^{131} in the form of compound X, a different result was observed. Whether the samples were heated with or without the caprylate ion, from 80 to 95 per cent of the I^{131} was found in the precipitate. Ultraviolet absorption measurements on the same samples showed that the albumin was precipitated only in the absence of caprylate. These results further suggest that compound X is neither an iodinated albumin nor an iodine-containing substance bound to serum albumin.

VI. *Iodinated Constituents in Compound X Hydrolysate*

All the albumin samples containing compound X were hydrolyzed and the hydrolysates were analyzed for I^{131}-labeled substances. Hydrolysis was carried out with $Ba(OH)_2$, 2N-6N HCl, crystallized trypsin (Armour) or crude pancreatin. Crude pancreatin was

TABLE 3. EFFECT OF CAPRYLATE ION ON HEATED* SERUM ALBUMIN, COMPOUND X AND IODO-ALBUMIN†

Sample	Hours after dose	Na caprylate (0.2 M)	Per cent total I^{131} in		Per cent total albumin‡	
			Ppt.	Supernat.	Ppt.	Supernat.
HSA (Cohn Fr. V)	—	Present	—	—	7.3	92.5
		Absent	—	—	97.9	2. 0
K.M.-I	24, 48	Present	88.7	10.3	—	93.6
		Absent	91.2	7.7	—	2.7
K.M.-II	24, 48, 96, 144	Present	86.9	12.0	—	94.0
		Absent	93.8	5.4	—	4.7
M.G.-I	48	Present	90.6	9.2	—	96.3
		Absent	96.3	1.6	—	4.3
E.P.-I	24, 48	Present	83.4	16.0	—	93.4
		Absent	88.2	11.8	—	3.3
E.P.-II	24, 48	Present	90.4	8.9	—	95.1
		Absent	96.1	2.6	—	2.8
HSA-I^{131}	—	Present	1.8	97.0	3.0	96.2
		Absent	94.2	5.1	96.7	1.6

* Heated at $67 \pm 2°$ C. for twenty-four hours.

† Each value represents the average of the individual values of albumin fractions of serum obtained at different hours after the dose of I^{131}.

‡ Measured by ultraviolet spectroscopy (275 mμ).

found to provide the best digestion, since it left the least amount of I^{131} in the unhydrolyzed protein fraction and at the same time caused minimal deiodination of the substrate. In all the subsequent experiments the following procedure was carried out: A portion of the albumin fraction (about 100 mg.) dissolved in 3.0 ml. of a 2.5 per cent $NaHCO_3$ solution at pH 8.8 was incubated at 37° C. with 5.0–7.0 mg. of Viokase powder (pancreatin, Viobin Corporation) and 2 drops of toluene. After incubation for twenty-four to forty-eight hours, 50–100 micrograms each of potassium iodide, thyroxine, triiodothyronine, diiodotyrosine and monoiodotyrosine were added as carriers to the contents of the tube, and the pH then brought to 3.0 ± 0.1 with diluted HCl. From three to five extractions were carried out with *n*-butanol saturated with 0.05 N HCl and the radioactivity was measured in the aqueous and organic phases. If the butanol had less than 80 per cent of the total I^{131}, more extractions were performed or the sample was discarded. All butanol extracts used for analysis contained 85–92 per cent of total I^{131}. The extracts were evaporated to dryness under reduced pressure (10 to 15 mm. of Hg) at $25 \pm 5°$ C. and the residue was redissolved in 0.2 ml. of *n*-butanol.

The concentrated hydrolysates were analyzed by chromatography in the acid and alkaline butanol systems and in the collidine system. In all these chromatograms there was no more than 5 to 10 per cent of the total I^{131} at the origin, indicating almost complete hydrolysis. The major part of the radioactivity (from 55 to 80 per cent) was identified as monoiodotyrosine. From 10 to 25 per cent of I^{131} was found in the position taken by thyroxine in the three solvent systems. A very small amount (2 to 10 per cent) of I^{131} was found in butanol-acetic acid chromatograms to have migrated to a position different from that of any of the carriers. This last radioactive fraction, which was designated as "F," did not show up as a distinct peak in the butanol-dioxane-NH_3 and collidine-H_2O system chromatograms. In order to evaluate the possibility that one or more of these three radioactive fractions could have been produced during concentration or chromatography, a larger preparative chromatogram was prepared in the butanol-acetic acid system. The areas of the three peaks were cut out and eluted with 10 per cent NH_4OH. The eluates, after concentration to about 0.2 ml., were rechromatographed in each of the three solvent systems, the radioactivity recorded, and the I^{131} peak compared with the position of those for the carriers present. All of these chromatograms showed only one peak—in the same position as when analyzed before elution. The single exception was the I^{131} from the eluate containing F, which yielded a smear and not a sharp peak in the butanol-dioxide-NH_3 and collidine-H_2O systems.

For further definition, two-dimension chromatography was performed as follows: The hydrolysates of the different albumin fractions were analyzed, using the butanol-acetic acid and the butanol-dioxane-ammonia systems as the two developing systems in the presence of the usual carriers. A radioautograph (Kodak radiographic no-screen film) was made from each bi-dimensional chromatogram and the positions of radioactive spots were compared with those of the carrier spots. A typical bi-dimensional autoradiograph is reproduced in Figure 3.

Of the 3 fractions described earlier, the component F is not as clearly seen in the photographic reproduction as in the original autograph. Besides these 3 a new radioactive spot must have been included with monoiodotyrosine in the uni-dimensional chromatographs. Figure 3 also shows the absence of diiodotyrosine and triiodothyronine—iodo-amino acids normally present in thyroglobulin.

For quantitation, the fraction of total hydrolysate I^{131} in each major component was determined by measuring the area occupied by the corresponding peak in the one-dimensional chromatogram. In 1 case (K.M.-II) it was possible to isolate enough labeled serum thyroglobulin for study. The gamma-globulin fraction (Cohn method—10) was hydrolyzed at the same time and in the same manner as described for compound X. In Table 4 are listed the data obtained on the fractional distribution of I^{131} in the amino acids of the hydrolysates of compound X and serum thyroglobulin.

The ratio of I^{131} in the iodothyronine fraction to that in the iodotyrosines may be compared for compound X and serum thyroglobulin. For compound X this ratio did not appear to vary with the time that had elapsed after the dose of radioiodine. In the serum thyroglobulin, on the other

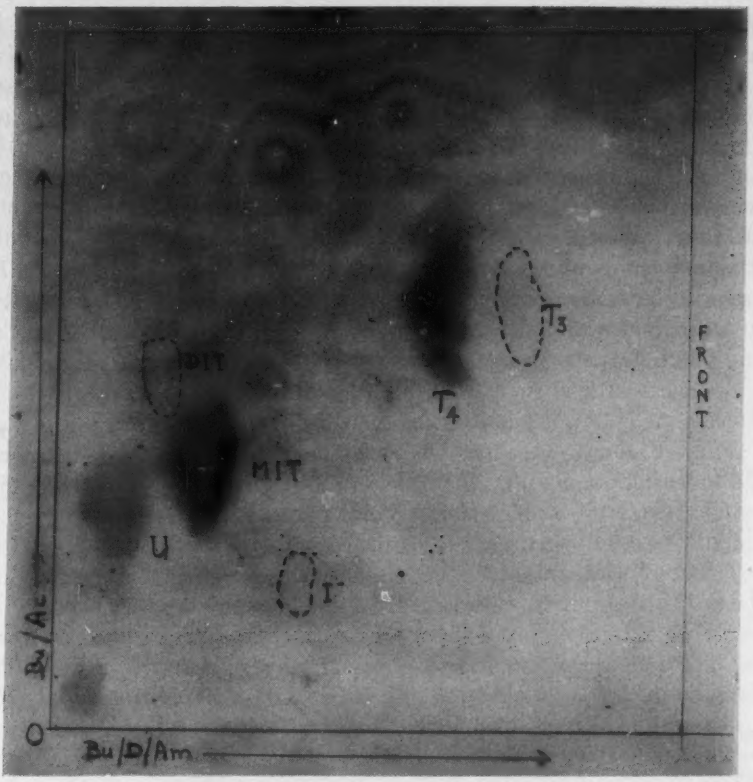

FIG. 3. Radioautogram of two-dimensional chromatography of the hydrolysate of I^{131}-labeled compound X, using butanol-acetic acid (Bu-Ac) and butanol-dioxane-ammonia (Bu/D/Am) as the developing solvent systems. The areas surrounded by the dotted line represent the position of substances absent in the hydrolysate (position known from the carriers added).

hand, there was an increase in the relative amount of I^{131} in thyroxine and triiodothyronine compared to that in iodotyrosine-I^{131}, with the passage of time.

DISCUSSION

These studies confirm the presence of a new iodinated compound in the serum of patients with cancer of the thyroid, as described by Robbins *et al.* (1) and by Horst and Roesler (16). In our series of patients, the same characteristics have been observed for the isolated albumin fraction of the serum as those reported by Robbins *et al.* for whole serum containing compound X.

The ultracentrifuge data perhaps illustrate best that compound X is a homogeneous substance and that it is the same from individual to individual. Multiple sampling of the upper compartment will disclose gross heterogenicity, if present, and there was no indication of this. Furthermore, the $S_{20,w}$ appeared to be the same in 2 patients and not significantly different from results reported earlier from this laboratory on 3 other subjects. The experiments with rabbit anti-albumin anti-serum and the experiments with caprylate ion on the thermal stabilization of albumin definitely distinguish compound X from an iodinated albumin. It is of interest that these reactions were specific, whereas electrophoresis at pH 8.6 and 4.5

TABLE 4. QUANTITATIVE CHROMATOGRAPHIC ANALYSIS OF HYDROLYSATE OF COMPOUND X

Patient	Hours after dose	Compound X						Serum T_4*
		Per cent total I^{131} distributed in					Ratio I^{131} T_4/MIT+DIT	Ratio I^{131} T_4/MIT+DIT
		I^-	MIT	DIT†	T_4	F		
K.M.-I	24	4.1	72.6	—	21.4	4.8	0.29	—
	48	3.3	69.9	—	19.8	6.4	0.28	—
K.M.-II	24	—	63.0	4.0 (?)	22.0	11.1	0.32	0.33
	48	—	66.2	—	24.3	8.0	0.34	0.39
	96	—	70.0	2.0 (?)	20.6	8.1	0.29	0.63
	144	1.1	72.8	—	19.5	5.5	0.28	0.65
E.P.-I	24+48	9.9	67.1	—	12.4	7.5	0.19	—
E.P.-II	24+48	—	64.1	—	14.1	8.9	0.22	—

* Serum thyroglobulin (gamma-globulin fraction) hydrolysates used for comparison.

† The values were obtained from peaks that were difficult to distinguish from the tail of the MIT peak, and do not confirm the presence of DIT in compound X.

and most commonly used methods for protein fractionation did not distinguish these two substances. It remains an unlikely possibility that compound X is a substance very firmly bound to albumin in such a way as to alter the binding of caprylate to albumin and also to alter the immunologic specificity of albumin. From a consideration of molar ratios, this appears to be most unlikely. Albumin is present in serum in a concentration of about 0.7×10^{-3} M. The concentration of compound X can only be inferred. The serum of these subjects usually contained iodine in a concentration of 5–10 micrograms per 100 ml. Considering only iodine and assuming only 1 iodine atom/mole of compound X, the concentration in serum of this substance must be about 0.5×10^{-6} M (molecular weight in the range of 60,000 from $S_{20,w}=4.3$). Therefore, it seems that no more than 1 molecule of compound X would be bound to any molecule of albumin. This site then must be identical with the site of caprylate binding and that

of antigen-antibody interaction. However, in the foregoing experiments the samples of albumin used for the immunologic studies were free and also stabilized with 0.02 M caprylate. In spite of this, the antigen-antibody reaction occurred in all cases with precipitation. Hence, the caprylate-binding and antigen-antibody interaction sites in the molecules are different. This makes it very unlikely that compound X is bound to serum albumin.

The results of hydrolysis of compound X were similar to those previously reported (1). The absence of diiodotyrosine in the presence of substantial amounts of monoiodotyrosine is surprising, and is perhaps even more unusual in view of the fact that a substance with the mobility of thyroxine was found. The presence of these 2 iodo-amino acids as constituents of a protein could not be accounted for by Harington's theory (17) that 1 molecule of thyroxine is derived from the condensation of 2 molecules of diiodotyrosine present in a natural or artificial iodoprotein. Very recently, however, Roche *et al.* have reported finding 3:3′-diiodothyronine in thyroglobulin and in blood (18). The chromatographic mobilities of 3:3′-diiodothyronine are such that, in the systems used in our experiments, it cannot be unequivocally distinguished from thyroxine. The possibility is open, therefore, that monoiodotyrosine and 3:3′-diiodothyronine (possibly derived from a condensation of 2 molecules of the former) are the main iodo-amino acids present. Diiodotyrosine and thyroxine are absent in compound X because some factor involved in the second step of a process Tyrosine→MIT→DIT is missing at the site of formation of the abnormal compound. Only a few reports have described iodoproteins containing monoiodotyrosine and lacking diiodotyrosine. One of the most convincing is the observation of Taurog *et al.* that the incubation of I^{131} with thyroid homogenates leads to the formation of a "thyroprotein" containing only monoiodotyrosine, whereas incubation of whole slices yields a protein with both monoiodotyrosine and diiodotyrosine (19).

The early appearance of compound X in the blood, as shown in Figure 2, only suggests that it is turned over rapidly in the blood, but gives no information as to its turnover time in the tissue where it is formed. The late appearance of thyroglobulin in blood after large doses of I^{131} has been noted before, and seems due to the length of time required to produce a degree of radiation damage to the thyroid follicular cells sufficient to permit leakage of this large protein from the follicle. No good explanation can be offered for the relatively constant ratio of I^{131} fractions T_4/MIT+DIT in the hydrolysate of compound X. In particular is this puzzling when it is taken into account that thyroglobulin isolated from the same subject showed the usual increase in the radioactivity of iodinated thyronines at the expense of iodinated tyrosines. It is possible that compound X and thyroglobulin are formed by different cells, and that an intrinsic peculiarity

of compound X formation is a turnover so rapid that there is no time for the second step of iodination of tyrosine in the molecule.

It has been previously shown that compound X may be found in about 60 per cent of subjects with cancer of the thyroid, and that it has not been found in normal subjects or those with nonmalignant disease of the thyroid (1). The present study sheds no light on these observations.

SUMMARY

An iodinated substance (compound X) found in the blood of certain patients with cancer of the thyroid has been studied. This substance appears to be homogeneous upon ultracentrifugation, and is similar in all cases studied. Its sedimentation constant is $S_{20,w} = 4.2$–4.3. Most of the analytical procedures do not separate compound X from the albumin fraction of the serum. However, compound X is not protected from thermal precipitation by sodium caprylate nor is it precipitated by rabbit anti-albumin antiserum. It can be hydrolyzed by trypsin to yield the iodinated amino-acid, monoiodotyrosine, and another amino-acid that may be thyroxine. Two other iodinated substances released after hydrolysis have not been identified.

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AN UNUSUAL IODINATED PROTEIN OF THE SERUM IN HASHIMOTO'S THYROIDITIS*

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PROTEIN-BOUND iodine may exist in forms other than thyroxine. Man and associates (1) found that patients receiving Lugol's solution usually had a significant amount of serum iodine that was precipitable together with proteins (therefore not being inorganic iodide) but was not soluble in butanol (therefore not being thyroxine). Danowski and coworkers (2) made the same observations on rats given iodides or iodine.

Robbins and associates (3, 4) have identified thyroglobulin in the serum after therapy with radioiodine (doses of 7 to 241 millicuries). This component was found in only small amounts in the serum of patients treated for hyperthyroidism; however, in about half the patients who had malignant lesions of the thyroid, a portion of the radioiodine precipitated along with proteins was identified as thyroglobulin. Robbins' group characterized this protein as having the following properties: (a) insoluble in butanol and, therefore, nonmobile in chromatographic systems using butanol; (b) salting-out characteristics comparable to those of purified thyroglobulin derived from the thyroid, and (c) ultracentrifugal sedimentation rate faster than that of normal serum proteins.

We have found evidence for a substance resembling thyroglobulin in the blood of patients with lymphocytic thyroiditis. This substance can be demonstrated after the administration of tracer doses of radioiodine or by means of standard technics for the determination of protein-bound iodine without the use of radioiodine. This iodinated serum protein is not present normally, at least in readily measurable amounts. Its true identity has not been determined because only tracer doses of I^{131} were administered and, as a consequence, the concentrations of radioiodine in the serum were

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inadequate for detailed studies such as Robbins and his co-workers have been able to carry out on the serum of patients treated with massive doses of I^{131}. The designation "thyroglobulin" implies nothing more than that the serum contained a protein labeled with iodine, the iodinated component being insoluble in butyl alcohol. It might equally well be the substance designated as "compound X" (5) or some still different substance. Since the I^{131} was administered as sodium iodide and it was recovered in bound form, the assumption of thyroidal involvement is made.

MATERIALS AND METHODS

Thirty-eight patients (all female) with Hashimoto's thyroiditis (struma lymphomatosa) have been studied at the Mayo Clinic during the last two years. The diagnosis in 20 of these patients was verified at the time of operation on the thyroid. In the other 18, the diagnosis was made on definite clinical grounds, namely the presence of a firm "rubbery" goiter and often a low basal metabolic rate or the presence of clinical myxedema in addition. However, since pathologic examination of sections of the thyroids was not made in these 18 patients, the diagnosis of Hashimoto's thyroiditis must be considered to be probable rather than proved.

An additional 14 patients (female) who had acute diffuse (granulomatous) thyroiditis were studied for comparison; the diagnosis in 5 of these was verified at operation, whereas the diagnosis in the other 9 was made on clinical grounds alone.

Most of the patients studied received 300 or 500 microcuries (μc.) of I^{131} orally.[1] The 24-hour thyroidal uptake of I^{131} was determined on the next day and a sample of blood was drawn for measurement of radioiodine and assays of stable iodine. In a few instances, the blood was drawn for iodine studies before administration of I^{131}. Samples of thyroid tissue were obtained at the time of operation in 9 patients.

Thyroidal uptake. In vivo measurements of thyroidal uptake were performed in the Section of Therapeutic Radiology. Uptakes determined eighteen to thirty hours after administration of I^{131} are designated as "24-hour uptakes."

Stable-iodine assays. These were performed in the Section of Biochemistry. Protein-bound iodine (PBI) was determined by the dry-ash technic on the Somogyi protein precipitate from serum, based on the Barker method (6). Butanol-extractable iodine (BEI) was measured by the same technic on either the *n*-butyl alcoholic extract of the precipitated serum proteins after acidification with hydrochloric acid or the butanol-insoluble residue, or both. With this technic, it was found that an average of 95 per cent of PBI in normal persons is extractable in butanol.

Radioiodine assays of serum. The amount of radioiodine in serum was measured in a sodium-iodide (thallium-activated) scintillation crystal of the well type. Its sensitivity at the usual settings and for a volume of 1 ml. was 16,000 counts per second (cps) per microcurie of I^{131} over a background of about 4 cps.

The content of I^{131} in 1 ml. to 6 ml. of whole serum was measured. The proteins were precipitated by the Somogyi technic, washed twice and then reassayed for I^{131} (PBI^{131}). To the protein precipitate was added a volume of 2N hydrochloric acid equal to one third the volume of the original serum; this was sufficient to dissolve the zinc hydroxide and proteins and reduce the pH to about 2. A volume of *n*-butyl alcohol at least twice the volume of the original serum was added slowly, with stirring; the proteins thus were

[1] Use of I^{131} was authorized by the Atomic Energy Commission.

reprecipitated. After centrifugation, four zones were evident, namely the supernatant butanol containing the serum pigments, a white layer of precipitate, an aqueous layer and, at the bottom, another small zone of precipitate. After the layer of butanol was decanted, more butanol was added, with thorough stirring. After centrifugation and decantation, a third extraction with butanol was carried out. At this stage, the aqueous layer had disappeared and the precipitate was firmly packed in the bottom of the tube. This extracted precipitate was assayed for I^{131} ($PBI^{131} - I^{131}$ of the extracted precipitate $= BEI^{131}$).

The values of I^{131}, expressed as percentages of the administered dose per liter of serum, were corrected for physical decay of I^{131} to the time of administration of the dose to the patient. Where S is the I^{131} of the whole serum (total I^{131}), P is the I^{131} precipitated along with proteins (PBI^{131}) and B is the butanol-insoluble residue (thyroglobulin I^{131}), the following calculations were made: S − P = inorganic iodide^{131}; P − B = thyroxine I^{131}.

Control studies with radiothyroxine or radiotriiodothyronine added to nonradioactive serum revealed that at least 98 per cent of both thyronines was precipitable by the Somogyi technic, that 98 to 99 per cent of the triiodothyronine was extractable by acid butanol, but that only 93 to 95 per cent of the thyroxine was extractable. As a result, any value for thyroglobulin less than 10 per cent of that for thyroxine in the same serum may represent only unextracted thyroxine. When NaI^{131} was added to serum, 1.5 to 2.3 per cent was retained in the twice-washed Somogyi precipitate, but only 0.1 to 0.3 per cent remained in the precipitate after acid-butanol extraction.

To differentiate the thyronines in the butanol extracts of serum, the butanol supernatant portions were pooled and reduced almost to dryness in vacuo at less than 40° C. The tarry residue was then subjected to paper or kieselguhr-column chromatography. Greater loss of I^{131} occurred if the residue was dried completely and then re-extracted.

Paper chromatography. The ascending technic of Gross and co-workers (7) was used. N-butyl alcohol and dioxane were equilibrated with 2N ammonium hydroxide (volumes of 4:1:5). Redistilled butanol and dioxane were used (8). Radioactivity along the chromatographic paper strip was determined by (a) autoradiography, using "no-screen" Kodak x-ray film, (b) scanning the strip with a Geiger-Müller tube connected to an automatic recording device, or (c) cutting the strip into segments that were individually counted in a well counter. Known samples of iodide (tested with starch), thyroxine and triiodothyronine (tested with ninhydrin) had mobility (Rf) values of about 0.35, 0.45 and 0.55, respectively.

Column chromatography. The technic of Gross and Pitt-Rivers (9), as modified by Braasch and associates (10), was used. The effluent did not pass directly to a fraction collector but was carried through a tube wound around a sodium-iodide scintillation crystal and thence to the fraction collector. Thus, the radioactivity was determined and recorded continuously. Good agreement was found for the various radioactive zones as determined by planimetry of the graphic record and by actual assay of the collected fractions of effluent.

Radioiodine assay of thyroid gland. As soon as the thyroid gland was excised surgically, portions of it were wrapped in saline-moistened sponges. The gland was cut into small bits and then homogenized with phosphate buffer (M/15 and pH 8). Hydrolysis with trypsin was continued for about four days by the method of Braasch and coworkers; at its conclusion, 2N hydrochloric acid was added in a volume about one third that of the digestion mixture. Three extractions with *n*-butyl alcohol were carried out, as for serum. The alcoholic supernatant portions were pooled and then prepared for chromatography as already described.

As a control on the hydrolytic procedure, *l*-thyroxine labeled with I^{131} was added to a thyroid gland free of I^{131}. After hydrolysis, the butanol extract was subjected to chromatography through a kieselguhr column. The thyroxine zone of the effluent fluid contained 95.1 per cent of the I^{131}; none was in the triiodothyronine zone; 4.9 per cent was in the iodide zone; and only trace amounts were in the zones ascribed to diiodotyrosine and monoiodotyrosine. For comparison, the values obtained by Braasch and colleagues have been used. This group examined 9 thyroid glands that were histologically normal and that contained I^{131}. Excluding from the calculation that amount of I^{131} retained on the column, they found that, on the average, 15.9 per cent of the I^{131} was thyroxine, 1.1 per cent triiodothyronine, 7.6 per cent iodide, 43.0 per cent diiodotyrosine and 32.3 per cent monoiodotyrosine.

Electrophoresis of whole serum. This procedure was performed in the Section of Biochemistry, and we are indebted to Mr. B. F. McKenzie for advice concerning the methods. From 10 to 50 microliters of serum was applied to strips of 3MM paper 2.5 cm. in width; electrophoresis was carried out at room temperature by a technic described previously (11). The strips were dried at room temperature and scanned for radioactivity. Sometimes a portion was excised, heated and stained with bromophenol blue to identify the zones of protein; the unstained portion was then cut into areas equivalent to the bands of protein. The radioactivity of these pieces was determined in a well counter.

RESULTS

The results of the studies on the 38 patients who had Hashimoto's thyroiditis are listed in Table 1. The records are arranged in order of increasing ratio of butanol-soluble (thyroxine) or butanol-insoluble (thyroglobulin) organic I^{131} in the serum.

Based on control studies, which showed that more than 90 per cent of the thyroxine I^{131} in serum is soluble in acid butanol, the finding of thyroglobulin I^{131} in the serum of at least the first 30 patients is probably significant, that is, the thyroxine:thyroglobulin ratio was considerably less than 10:1. Furthermore, in about one third of the patients (Cases 1 through 12), the concentration of thyroglobulin I^{131} in the serum actually exceeded that of radiothyroxine. Cases 9, 15 and 17 furnish confirmatory values from the standpoint of stable serum iodine.

In a recent study (12) of a large series of normal persons, the concentration of protein-bound I^{131} in serum twenty-four hours after administration of I^{131} ranged from 0.014 to 0.167 per cent of the dose per liter of serum. The concentration of thyroglobulin I^{131} alone equaled or was greater than the upper limit of normal in 7 of the patients in the present study, notably 0.854 per cent of the dose per liter (Case 8), 0.377 per cent (Case 18), 0.322 per cent (Case 27) and 0.237 per cent (Case 1).

Twenty-three of these 38 patients with lymphocytic thyroiditis were thought to be euthyroid; the remaining 15 were considered as hypothyroid. The concentration of thyroxine I^{131} in the serum of 12 of the myxedematous patients was determined one day after administration of the

TABLE 1. CLINICAL AND LABORATORY DATA ON 38 FEMALES WITH HASHIMOTO'S THYROIDITIS

Patient				Stable iodine (μg./100 ml.)			Thyroidal uptake (% of I^{131} dose‡)			Serum I^{131} (% of dose per liter)				
Case No.*	Age (yrs.)	Thyroidal state†	BMR (%)	PBI	BEI	Dose of I^{131} (μc.)	24 hrs.	48 hrs.	Days after dose	Total	Iodide	Thyroxine	Thyroglobulin	Thyroxine: thyroglobulin ratio
1*	35	Eu	−16	—	—	500	40		2	.508	.196	.075	.237	0.3
2*	17	Eu	0	3.1	—	68§	59§		§	100§	46§	16§	38§	0.4
3	35	Eu	−21	3.1	—	300	63		1	.369	.112	.073	.184	0.4
4*	34	Myx	− 8	2.5	—	300	31		1	.432	.257	.065	.110	0.6
5	27	Eu	− 4	—	—	300		41	2	.317	.043	.107	.167	0.6
6*	44	Eu	−17	3.7	—	500	49		1	.882	.695	.078	.109	0.7
7*	41	Eu	+ 4	—	—	300	33		1	.323	.202	.025	.036	0.7
8*	22	Eu	−18	—	—	300	—		2	1.600	.081	.665	.854	0.8
9*	44	Eu	−20	6.1	2.9	500	52		2	.221	.045	.077	.099	0.8
10	57	Myx	−18	1.4	—	500	9		1	1.282	1.139	.063	.080	0.8
11	33	Eu	+ 3	6.7‖	4.7	500	23		1	.458	.388	.032	.038	0.8
12*	52	Eu	− 6	4.1	—	300		33	2	.161	.052	.051	.058	0.9
13	74	Myx	−15	1.7	—	300		37	2	.537	.114	.229	.194	1.2
14*	51	Eu	−12	—	—	500	—		1	.356	.295	.034	.027	1.3
15	34	Myx	−24	1.3	0.1	300	4		1	1.501	1.408	.055	.038	1.4
16	37	Myx	−14	3.5	—	300	—		1	.964	.818	.087	.059	1.5
17	24	Eu	+ 2	8.5‖	4.6	300	—		1	.517	.482	.021	.014	1.5
18*	9	Eu	−11	5.6	—	300	76		1	1.012	.007	.628	.377	1.7
19*	32	Eu	− 3	4.3	—	500	28		1	.423	.337	.057	.029	2.0
20*	62	Eu	− 7	—	—	500	30		1	.255	.196	.040	.019	2.1
21*	50	Eu	0	3.7	—	500	15		1	.919	.854	.044	.021	2.1
22*	43	Eu	− 4	—	—	300	2		1	.967	.910	.041	.016	2.6
23	33	Eu	—	5.4	—	500	37		2	.326	.144	.132	.052	2.6
24	52	Myx	−32	—	—	500	3		1	1.146	1.114	.023	.009	2.6
25	58	Myx	−17	0.8	—	500	12		1	1.089	1.036	.039	.014	2.8
26*	33	Eu	−11	3.3	3.1	500	—		2	.247	.102	.105	.040	2.8
									4	.196	.007	.131	.058	2.3
27	24	Myx	−21	1.8	1.4	300		22	2	1.471	.224	.925	.322	2.9
28	41	Myx	−28	—	—	200	—		1	1.207	1.160	.036	.011	3.3
29	46	Myx	−17	5.6	—	300	18		1	.996	.941	.043	.012	3.6
30	50	Eu	−15	3.5	2.9	300	—		1	.320	.062	.209	.049	4.3
31	62	Myx	−17	1.3	—	500	33		3	.331	.107	.183	.041	4.5
									2	.160	.050	.093	.017	5.5
32	47	Eu	−17	—	—	300		16	4	.217	.014	.184	.019	9.7
									6	.250	.007	.214	.029	7.4
33*	42	Myx	−16	0.7	—	500	—		1	.998	.954	.038	.006	6.3
34	53	Myx	−16	1.3	1.3	500	8		1	.657	.605	.046	.006	7.7
35*	44	Myx	− 6	2.4	—	300	19		1	.516	.320	.176	.020	8.8
36*	55	Eu	+ 1	4.0	3.1	300	—		1	.568	.477	.082	.009	9.1
37*	56	Eu	− 5	4.4‖	3.9	500	30		1	2.484	.221	2.192	.071	30.9
									2	2.806	.141	2.580	.085	31.5
38*	36	Myx	−13	2.6		500	—		1	.406	.365	.041	0	∞

* Asterisk indicates that the diagnosis was made on a surgical pathologic basis.

† Eu = euthyroid clinically; Myx = myxedematous.

‡ At 24 hours, 35 per cent of the dose had been excreted in the urine in Case 8.

§ Received 68 μc. of I^{131} over a 7-day period; serum values are expressed as per cent of total I^{131} rather than as per cent of dose per liter of serum.

‖ Blood was drawn for analysis of stable iodine before administration of I^{131}.

dose; the resulting concentrations ranged from 0.023 to 0.176 per cent of the dose per liter, with a mean of 0.061; these values are comparable to those for normal persons. More curious are the occasional extremely

high values for serum thyroxine I^{131}, such as more than 2 per cent of the dose per liter in Case 37 (rechecked on a new sample of blood the next day), more than 0.9 per cent in Case 27 (myxedematous) and more than 0.6 per cent in Cases 8 and 18 (euthyroid).

The serums of 2 patients (Cases 23 and 26) were subjected to both column and paper chromatography. Although radioactivity was extremely weak, discernible I^{131} was found in only the thyroxine and iodide zones. The serums of these 2 patients also were treated electrophoretically; the radioactivity in each was localized almost entirely to two zones, namely the alpha globulins and the albumin. This is also true, in our experience,

TABLE 2. COMPARISON OF I^{127} AND I^{131} IN SERUMS OF 10 WOMEN WITH HASHIMOTO'S THYROIDITIS

Case	Ratios		Days after dose of I^{131}
	$BEI^{127}:PBI^{127}$	$BEI^{131}:PBI^{131}$	
15	.08	.59	1
9	.48	.44	2
17*	.54	.60	1
11*	.70	.46	1
36	.78	.90	1
27	.78	.74	2
30	.83	.81	1
37*	.89	.97	1
26	.94	.72	2
34	1.00	.88	1

* Blood collected for analysis of stable iodine before administration of I^{131}.

of the serum of patients with thyroidal carcinoma treated with I^{131} (thyroxine in the inter-alpha zone, thyroglobulin in the albumin). The alpha globulin:albumin I^{131} ratio in Case 23 was 2.4; it may be noted that the ratio by chemical fractionation was 2.6. The agreement in Case 26 was not so close; the thyroxine:thyroglobulin ratio in the four-day serum specimen as determined chemically was 2.3, whereas that determined electrophoretically was 1.4. It must be concluded that the organic I^{131} soluble in acid butanol is thyroxine or a very closely related substance, in order to allow such parallelism of action in three such different technics as paper and column chromatography and paper electrophoresis.

Determinations of butanol-extractable iodine were performed on the serums of 10 patients. The ratios of BEI and PBI of both stable (I^{127}) and radioactive (I^{131}) iodine are compared in Table 2. The agreement between the two ratios is good in most instances. This suggests that the radioiodine

TABLE 3. CLINICAL AND LABORATORY DATA ON 14 WOMEN WITH ACUTE DIFFUSE (GRANULOMATOUS) THYROIDITIS

Patient		BMR (%)	Stable iodine (μg./100 ml.)		Dose of I^{131} (μc.)	24-hour thyroidal uptake (% of I^{131} dose)	Serum I^{131} (% dose per liter)				
Case No.	Age (yrs.)		PBI	BEI			Days after dose	Total	Iodide	Thyroxine	Thyroglobulin
39	50	+ 4	4.7	—	300	17	1	1.661	1.593	.058	.010
40*	63	+10	6.9	—	500	12	6	.029	.006	.019	.004
41*	57	+ 6	7.5	—	500	6	1	.976	.945	.033	.008
42	50	+ 3	—	—	300	5	1	.419	.396	.015	.008
43*	41	− 1	8.7	—	500	3	1	1.058	1.019	.031	.008
44*	46	—	5.9	—	500	1	1	1.047	.905	.122	.020
45	39	+14	—	—	500	1	1	.196	.154	.025	.017
46*	74	+15	9.0	8.6	500	1	1	.773	.742	.021	.010
47	56	—	—	—	300	1	1	.467	.447	.012	.008
48	39	−10	—	—	500	1	1	.420	.365	.050	.005
49	45	− 4	—	—	500	1	1	.313	.288	.020	.005
50	61	+21	16.7	—	300	1	1	.422	.400	.019	.003
51	55	—	11.7	—	300	1	1	.364	.339	.025	0
52	43	−20	7.4	—	300	1	2	.209	.205	.004	0

* Surgical pathologic diagnosis of granulomatous thyroiditis.

compounds quickly reach equilibrium with the stable iodinated substances, since the specimens of blood were obtained one or two days after administration of I^{131}. A discrepancy between PBI and BEI was found in 2 patients with adolescent lymphocytic thyroiditis by Gribetz and co-workers (13).

Data on the 14 patients who had acute diffuse thyroiditis are listed in Table 3. Significant but small amounts of thyroglobulin I^{131} appeared in the serum in a few patients. Only in Case 44 was an increased concentration of thyroxine I^{131} found in the serum.

In Table 4 are summarized the column-chromatographic values obtained in a study of 9 thyroid glands hydrolyzed by means of trypsin. The values in patients who had Hashimoto's thyroiditis do not appear to differ significantly from the normal range determined by Braasch and coworkers. The scarred zone in Case 40 (granulomatous thyroiditis) probably contained only I^{131}, the "thyroxine" either representing contamination from nearby tissue or, more likely, being the "forepeak" artifact which is difficult to distinguish from true thyroxine.

COMMENT

Analysis of the serum of patients with Hashimoto's thyroiditis has revealed the presence of a fraction of iodine insoluble in acid butanol in most patients whose disease has not yet progressed to complete athyreosis. This finding, sometimes striking when values for stable PBI and BEI are compared, generally is even more pronounced when radioiodine in the serum is studied the first few days after administration of a tracer dose of radioiodine.

Other butanol-insoluble compounds of iodine have been reported after prolonged administration of Lugol's solution or after use of I^{131} for thyroidal carcinoma. Whether these three compounds are the same is not known. One might conceive of thyroidal thyroglobulin being released to the blood stream as a result of the pathologic process of lymphocytic thyroiditis,

TABLE 4. CHROMATOGRAPHIC DISTRIBUTION OF I^{131}-LABELED COMPOUNDS FROM HYDROLYZED THYROID GLANDS*

Case	Days between dose of I^{131} and operation	Per cent of total I^{131} in column effluent				
		Thyroxine	Triiodothyronine	Iodide	Diiodotyrosine	Monoiodotyrosine
2	1†	21.2	2.4	4.6	50.3	21.5
6	4	5.2	1.1	17.4	29.9	46.4
9	2	13.3	1.7	10.4	41.2	33.3
14	1	10.8	0	6.4	51.5	31.2
26 Pink zone	2	30.0	0.7	2.5	20.2	46.6
26 Gray zone	2	34.3	0.5	0.9	26.0	38.4
35	1	15.8	0.2	20.8	24.1	39.2
36	1	23.2	1.9	20.5	23.1	31.3
37	2	20.2	0.7	14.6	32.9	31.6
40 Pink zone	5	4.7	trace	5.2	41.6	48.4
40 Scarred zone	5	4.2	0	95.8	trace	trace
Average of 9 normal glands		*15.9*	*1.1*	*7.6*	*43.0*	*32.3*

* Case 40 represents granulomatous thyroiditis; the remainder represent Hashimoto's thyroiditis.

† One day after last dose of I^{131}.

similar to its release from disintegrating malignant tumors undergoing radiation therapy.

It has been suggested (14) that a compensatory increase in thyrotropin stimulation occurs as the thyroid fails in Hashimoto's thyroiditis. An attempt to inhibit this function of the pituitary was made in Case 2. This patient, who had an initial thyroidal uptake of 59 per cent of the dose in twenty-four hours, was treated with daily doses of 50 micrograms of *l*-triiodothyronine; after two days the uptake of a new dose of I^{131} was only 36 per cent, and the uptake of a third dose three days later was only 24 per cent. Since thyroidal uptake of I^{131} is believed to be suppressed only in those persons whose thyroid glands are under the domination of the pituitary, unlike patients with Graves's disease (15), one might assume

that the accelerated initial uptake in this patient was of pituitary origin. Two patients with Hashimoto's thyroiditis, who were not included in this series because blood studies were not made, were given intramuscularly doses of 10 units of bovine thyroid-stimulating hormone (TSH) (16). One of the 2 responded with a significantly increased thyroidal uptake of I^{131}.

If the production of thyrotropin is increased, this might precede rather than follow the pathologic process of the thyroid gland and thus might be the cause of the increased uptake of radioiodine in some patients with Hashimoto's thyroiditis. This in turn might account for the increased concentration of radiothyroxine in the serum of certain of these patients. Such patients logically might be expected to be hyperthyroid clinically, but all in this series were either euthyroid or hypothyroid and the serum PBI or BEI level was normal or decreased in all instances. To correlate increased uptake of radioiodine and increased concentrations of radiothyroxine in the serum with absence of hypermetabolic states and normal or decreased values for serum thyroxine, one might consider the following possibilities: (a) the "radiothyroxine" is in fact a closely related thyronine with limited metabolic activity, (b) the peripheral site of action of thyroxine is relatively insensitive to this hormone in this disease, or (c) the iodine spaces of the body, particularly in the thyroid, are so limited that the increased uptake of I^{131} by the thyroid and the hypersecretion of thyroxine I^{131} merely reflect an unusually high specific activity of the stable iodide and thyroxine.

Regardless of these theoretic aspects, a combination of normal or increased thyroidal uptake of I^{131}, normal or decreased values for serum PBI concentration and a decreased basal metabolic rate—especially if associated with a significant amount of thyroglobulin I^{131} in the serum—may be a guide leading to the diagnosis of Hashimoto's thyroiditis. Conversely, in acute diffuse thyroiditis one usually finds no thyroidal uptake of I^{131}, normal or increased values for the basal metabolic rate and serum PBI level, and a greatly increased erythrocytic sedimentation rate.

SUMMARY

The serums of 38 patients who had Hashimoto's thyroiditis and 14 who had acute diffuse (granulomatous) thyroiditis were studied after administration of tracer doses (68 to 500 microcuries) of I^{131}. A significant amount of I^{131} that was precipitable together with proteins and insoluble in acid butanol was found in most patients with Hashimoto's thyroiditis who had not progressed to the point of athyreosis. An occasional patient also had abnormally increased concentrations of thyroxine I^{131} or of some closely related compound.

Butanol extracts of trypsin-hydrolyzed thyroid glands from 8 patients

with Hashimoto's thyroiditis and 1 patient with granulomatous thyroiditis were studied by chromatography. The distribution of radioiodinated compounds was comparable to that in normal thyroid glands.

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NODULAR LESIONS OF THE THYROID GLAND IN CHILDREN*

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REPORTS in the literature indicate that there has been considerable variation in the incidence of diseases that produce nodular goiter in children (1). Carcinomas of the thyroid gland in children have been recognized with increasing frequency, whereas benign adenomas appear to be occurring less frequently. In an effort to ascertain the relative incidence of conditions that produce nodular enlargement of the thyroid gland in children, we have reviewed the records of 130 patients 14 years of age or younger who had nodular goiter and were seen at the Mayo Clinic in the years 1908 through 1955.

The subject of nodular goiter in children was reviewed by one of us (Kennedy) in 1940 (2). Pemberton and Black included information about children with nodular goiter in their report published in 1944 (3). Conditions associated with diffuse symmetrical enlargement of the thyroid gland, such as exophthalmic goiter and adolescent or colloid goiter, are not considered in our report. The data on the distribution of the 130 patients of this series according to the conditions that produced nodular goiter and according to sex are listed in Table 1, and the distribution according to year of diagnosis is shown in Figure 1.

ADENOMATOUS GOITER

Adenomatous goiter is nodular enlargement of the thyroid gland due to the presence of one or more benign adenomas within its substance, and this diagnosis was made in 68 of the 130 patients in this series. A clinical diagnosis of single adenoma of the thyroid was made in about one third of the 68 patients, and a diagnosis of multiple adenomas in a colloid goiter

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TABLE 1. NODULAR ENLARGEMENT OF THE THYROID GLAND IN INFANTS AND CHILDREN SEEN AT THE MAYO CLINIC IN THE YEARS 1908 THROUGH 1955: DISTRIBUTION OF PATIENTS ACCORDING TO CAUSE OF ENLARGEMENT AND ACCORDING TO SEX*

Cause	Boys	Girls	Total
Adenomatous goiter	15	53	68
Lymphocytic thyroiditis	2	6	8
Goitrous cretinism	1	4	5
Congenital goiter	2	1	3
Carcinoma of thyroid	13	33	46
Total	33	97	130

* Prior to 1917 the ages of patients with goiter who were not operated on were not indexed. Because of this, children with nodular goiter who were seen at the clinic from 1908 to 1917 but who were not operated on could not be included in the study.

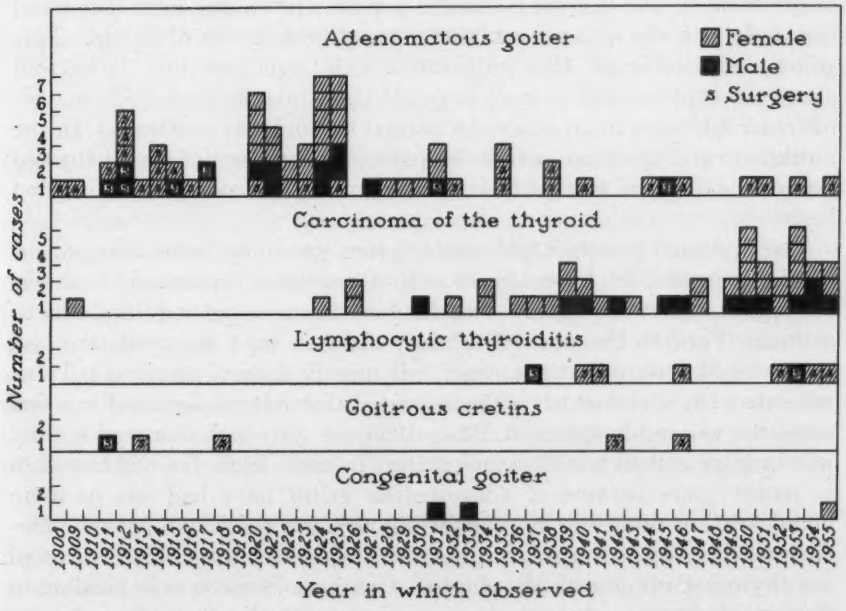

FIG. 1. Distribution of patients according to lesion and year of diagnosis. The diagnosis of carcinoma was made by histologic examination of surgically removed tissue, although not all patients were treated surgically.

was made in the remaining two thirds. In a few instances, attention was first directed to the goiter during the course of examination for unrelated conditions, but in most instances the presence of a goiter prompted the patient's visit to a physician. The adenomas varied in size and number from single tiny nodules to single or multiple lesions so large in some cases as to require removal for cosmetic or mechanical reasons, or both. The largest goiter that was removed surgically weighed 250 Gm. and consisted of multiple adenomas that had been enucleated from both lobes of the thyroid. The patients ranged in age from 4 through 14 years, but 56 of the 68 in this group were in the age group 10 through 14 years. The ratio of girls to boys was approximately $3\frac{1}{2}$ to 1.

In our experience, adenomatous goiter in children is rarely if ever associated with significant alteration of thyroid function. Hypothyroidism is known to have occurred in only 5 patients, and in each of these it followed surgical removal of the goiter. Hyperthyroidism was suspected in only 1 instance. This patient, a girl aged 7 years, was noted to have a nodular goiter at the age of $4\frac{1}{2}$ years. The goiter caused no symptoms until about four months before her admission to the Mayo Clinic in 1944, when the complaints were nervousness, irritability and sweating. She had no exophthalmos. The thyroid contained a nodule in the left lobe. The basal metabolic rate was +25 per cent and a tentative diagnosis of exophthalmic goiter was entertained. After preparation with Lugol's solution the thyroid gland was explored and a single large (24-Gm.) microfollicular and macrofollicular adenoma in an otherwise normal thyroid was enucleated. In the immediate postoperative period the patient was given desiccated thyroid but she has had no treatment since that time and has remained in good health.

The preferred treatment of adenomatous goiter in children is, in our opinion, surgical. We have arrived at this conclusion because of the rather striking change in the nature of the lesions that produce nodular goiter in children. Prior to the year 1935, many children were observed who had large colloid goiters that contained soft, poorly defined adenomas. These patients were often treated with desiccated thyroid or iodine and in a few cases the goiters disappeared. Since 1935, we have not observed a child with a large colloid adenomatous goiter. In most instances children seen in recent years because of adenomatous goiter have had one or more nodules in an otherwise normal-feeling thyroid gland. At present, carcinoma is the most frequently observed cause of nodular enlargement of the thyroid gland among the children seen here. Since it is impossible to distinguish benign adenoma from carcinoma of the thyroid except by histologic examination, we now urge surgical treatment in every case.

In this series of 68 children with adenomatous goiter, 34 (27 girls and 7

boys) were treated surgically before they reached the age of 15 years. The operation consisted of enucleation of one or more adenomas in 13 cases, removal of an entire lobe in 11 cases, and subtotal resection of both lobes in 10 cases. There were no hospital deaths. Evidence of hypothyroidism developed in 5 patients, in 3 of whom it developed after subtotal resection and in 2 after enucleation of adenomas. Twenty-five of the 34 children have been followed for periods that range from one to forty-two years after operation, and these were in good health at the time of last report, although 1 patient required a second operation for removal of a recurrent adenoma.

The remaining 34 patients with adenomatous goiter, all seen before 1936, were treated medically. Several of these patients refused surgical

TABLE 2. PATHOLOGIC TYPES OF ADENOMATOUS GOITER OBSERVED IN 34 CHILDREN TREATED BY SURGICAL EXCISION OF THE GOITER

Type of goiter	Cases
Mixed microfollicular and macrofollicular adenoma	23
Fetal adenoma	8
Colloid adenoma	2
Solid and trabecular adenoma (embryonal)	1
Total	34

treatment, which was advised after medical management failed to alter the size of the goiter. Six patients are known to have had surgical treatment subsequently, after periods varying from five to twenty years after the diagnosis of adenomatous goiter was established; 5 of these elected to have such treatment because of the size of the goiters, and the sixth had it because of hyperthyroidism that developed twenty years after the goiter was first noted. In 3 patients the nodules disappeared during treatment with iodine or desiccated thyroid, but in 6 others who were observed at irregular intervals for periods ranging from one to twenty-eight years the nodules were not altered by medication. Three patients died of causes unrelated to their thyroid disease. The remaining 16 patients have not been followed.

The benign adenomas removed surgically were divided into four pathologic types (Table 2). A single adenoma was found in 20 patients and multiple adenomas were found in 14. They varied in size, the largest measuring 6 cm. in diameter. The gross appearance of the cut surface varied considerably. Fetal adenomas characteristically had a semi-translucent myxomatous appearance, whereas the macrofollicular nodules contained

much colloid. Variable degrees of degenerative change, including hemorrhage, fibrosis and calcification, were noted. A few tumors were almost completely cystic.

The most common histologic pattern was that of microfollicular and macrofollicular adenoma (fetal and colloid adenoma), usually with macrofollicles filled with colloid (Fig. 2*a*). Some degree of papillary hyperplasia was seen in most adenomas of this type (Fig. 2*b*).

The second most common histologic pattern was that of fetal adenoma showing a predominance of miniature fetal acini (Fig. 2*c*). Adenomas composed entirely of large colloid-filled macrofollicles, the so-called colloid adenomas, were found in 2 cases. One tumor (Fig. 2*d*) showed a trabecular or embryonal pattern of solid cords with no follicular or colloid formation.

LYMPHOCYTIC THYROIDITIS

Lymphocytic (Hashimoto's) thyroiditis is an unusual cause of enlargement of the thyroid gland in children. It has been seen at the Mayo Clinic in 8 children (6 girls and 2 boys) whose ages ranged from 8 to 14 years (Table 3). Seven of the children were admitted because of goiters which had been present for periods varying from four months to eight years. In

TABLE 3. DATA ON CHILDREN WITH LYMPHOCYTIC THYROIDITIS

Case	Year seen	Age of patient (yrs.)	Sex	Basal metabolic rate (%)	Serum protein-bound iodine, (μg./100 ml.)	Thyroidal I^{131} uptake in 24 hrs. (% of dose)
1	1937	13	M	− 6	—	—
2	1940	10	F	+ 4	—	—
3	1941	14	F	−13	—	—
4	1946	10	F	− 8	—	—
5	1952	13	F	—	4.8	42.8
6	1953	11	M	− 8	5.4	44.7
7	1954	9	F	−11	5.6	76.4
8	1955	8	F	—	4.2	18.0

the eighth child the goiter was discovered during examination for an unrelated disease. None of these patients exhibited evidence of abnormal thyroid function.

Goiters resulting from lymphocytic thyroiditis vary considerably in size but are usually two to three times the size of the normal thyroid. The whole thyroid gland is enlarged, although the enlargement may be asymmetrical. Palpation of the goiter discloses it to be firm, easily outlined and somewhat irregular. The nodular feel imparted by the goiter is due to an exaggeration

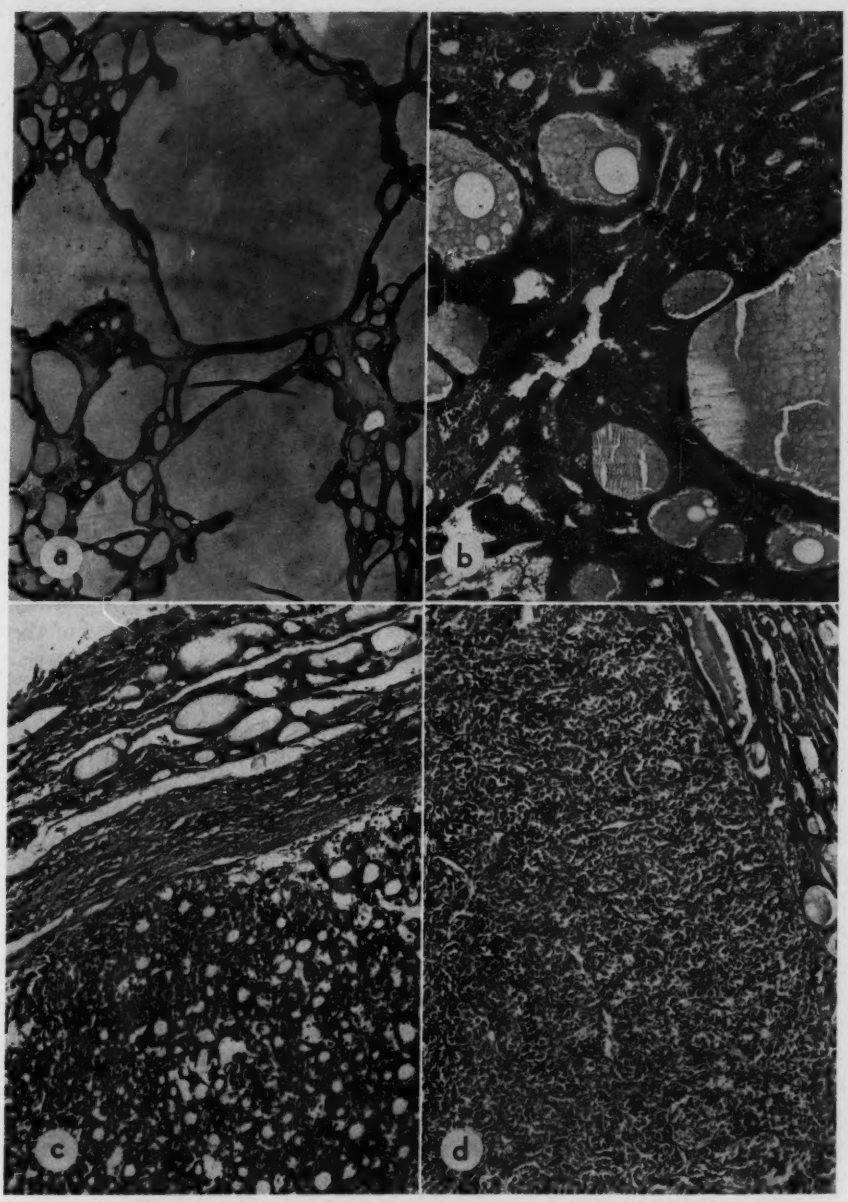

FIG. 2. Adenomatous goiter. Sections stained with hematoxylin and eosin. **a.** Microfollicular and macrofollicular adenoma (×50). **b.** Microfollicular and macrofollicular adenoma with papillary infolding (×110). **c.** Fetal adenoma showing microfollicles (×115). **d.** Embryonal (trabecular) adenoma (×115).

of the normal thyroid lobulation. Occasionally, a patient may complain of slight discomfort as the thyroid is palpated.

Lymphocytic thyroiditis is to be suspected in any euthyroid child with a firm irregular goiter, especially if study with a radioiodine tracer discloses a high uptake of I^{131} by the thyroid. Unfortunately, the diagnosis can be established with certainty only by histologic study. Therefore, only those patients in whom the diagnosis was established by histologic study are included in this report.

Three methods of treating lymphocytic thyroiditis have been recommended. These are i) surgical excision of the goiter (4), ii) the administration of desiccated thyroid (5), and iii) roentgen-ray therapy (6). Each of the patients (with lymphocytic thyroiditis) in this study was treated by subtotal thyroidectomy. There were no operative deaths. Hypothyroidism, satisfactorily controlled with desiccated thyroid, occurred in 7 of the 8 patients within four months after operation. We do not consider hypothyroidism a serious complication of surgical treatment, since it occurs as a consequence of the disease in many patients with thyroiditis.

The decision to perform subtotal thyroidectomy on children suspected of having thyroiditis has been based on the fact that carcinoma of the thyroid cannot be excluded in any given patient except by histologic study of an adequate biopsy specimen. Biopsy of the thyroid with the aid of the Silverman needle has been recommended (5) but has not proved satisfactory in our experience. Lymphocytic infiltration is not infrequently observed in areas surrounding a primary carcinoma in the thyroid, and it is possible that needle biopsy of such an area could lead to an erroneous diagnosis of thyroiditis in a patient with carcinoma.

Although we have had no experience in the treatment of lymphocytic thyroiditis in children with desiccated thyroid, experience gained among adults indicates that goiters do not always disappear after such treatment. As most children with lymphocytic thyroiditis have rather large goiters, we have also felt justified in urging subtotal thyroidectomy for cosmetic reasons. This operation adds little or no risk to that of surgical removal of enough thyroid tissue for histologic examination.

In the light of present concern about ionizing irradiation and its possible role (7) in the production of carcinoma of the thyroid gland in children, roentgen-ray therapy does not appear to be justified.

Pathologic examination in the 8 cases established the diagnosis of diffuse lymphocytic thyroiditis. On gross inspection the glands appeared to be moderately enlarged bilaterally. They were firm in consistency, and showed prominent lobulation and trabeculation on the cut surface. There was no adenoma in this group of patients. Histologically there was extensive lymphocytic and plasma-cell infiltration, both interfollicular and intra-

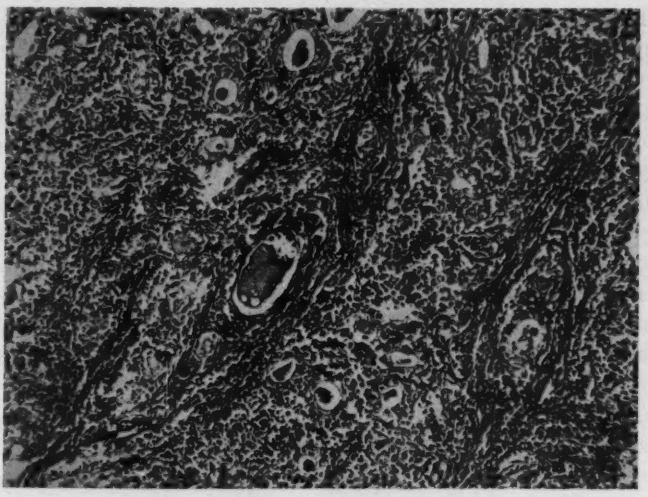

FIG. 3. Lymphocytic thyroiditis showing small follicles poor in colloid with associated lymphocytic and plasma cell infiltration (hematoxylin and eosin; ×125).

lobular (Fig. 3). Well-formed germinal centers were commonly present. Persisting follicles were of small size with lumens almost empty of colloid or containing macrophages. Oxyphilic epithelium was not observed in this series. In several cases, marked papillary infolding was noted. Fibrosis was not a prominent feature.

GOITROUS CRETINISM

In the United States cretinism associated with goiter exists as a rare familial disease. In patients with this disease the thyroid glands are unable to synthesize thyroid hormone but the particular defect in synthesis differs in different families. The thyroid usually begins to enlarge in infancy or early childhood, frequently becomes nodular and may reach enormous size by the time the child attains adolescence. Five children varying in age from 8 months to 14 years have been observed at the Mayo Clinic because of large nodular goiters associated with cretinism (Fig. 1). These patients represent all of the juvenile cretins with adenomatous goiter seen here, although there may be others in whom goiters have failed to develop because of adequate thyroid medication. There was considerable variation in the stigmata of cretinism, depending upon the age of the patient at the time treatment with thyroid hormone was started, the amount of hormone given, and perhaps the severity of the defect in synthesis of the hormone.

Each of the 5 patients underwent subtotal thyroidectomy. In 2 of these the operation was performed after several years of observation. Another

patient had had two previous operations for nodular goiter, and still another experienced recurrence of the goiter, which was removed six years after the first operation.

The treatment of goitrous cretins consists of the administration of adequate amounts of desiccated thyroid, in addition to surgical treatment for the goiter when indicated.

The surgically resected thyroid tissue or histologic sections were available for study in only 4 of the 5 goitrous cretins. Examination of the specimens in 2 cases disclosed moderate enlargement of the thyroid gland in which were seen, on the cut surface, multiple nodules that measured up to 3 cm. in diameter; the nodules were present in both lobes (Fig. 4*a*). Histologically the pattern of the nodules was either that of solid or trabecular (embryonal) adenoma or that of fetal adenoma (Fig. 4*b*), the former predominating. The intervening thyroid parenchyma was abnormal, containing small acini with little colloid formation; there was rather marked irregularity of nuclear size, suggestive of a degenerative process. In 1 case the intralobular and interfollicular connective tissue was increased in amount. In 2 cases the surgically removed specimen consisted mainly of fetal adenomas, and little or no parenchymal tissue was available for study.

CONGENITAL GOITER

Congenital goiter or diffuse symmetrical enlargement of the thyroid gland at the time of birth is seen rarely in the United States. In most instances the cause is unknown but the condition has been noted in infants born of mothers treated with antithyroid drugs (8) or iodides during the last trimester of pregnancy. Symptoms produced by congenital goiter are those of pressure on contiguous structures (4).

Congenital goiter has been recognized in only 3 patients (2 boys and 1 girl) at the Mayo Clinic (Fig. 1). All 3 were born of mothers who had been taking large doses of iodides. The goiters were described as being rather firm and nodular. One of the infants when examined at 2 years of age manifested evidence of mental retardation and cerebral palsy, but no evidence of thyroid dysfunction. A second patient was apparently well at 20 years of age, according to a report received from his grandmother. The third patient has not been traced.

Two of the patients were treated with iodides, and the third received desiccated thyroid.

CARCINOMA OF THE THYROID GLAND

Forty-six children 14 years of age or younger who had carcinoma of the thyroid gland were seen at the Mayo Clinic in the years 1908 through 1955 (Fig. 1). Thirteen were boys and 33 were girls. Our experience with this disease has been the subject of a recent report (9).

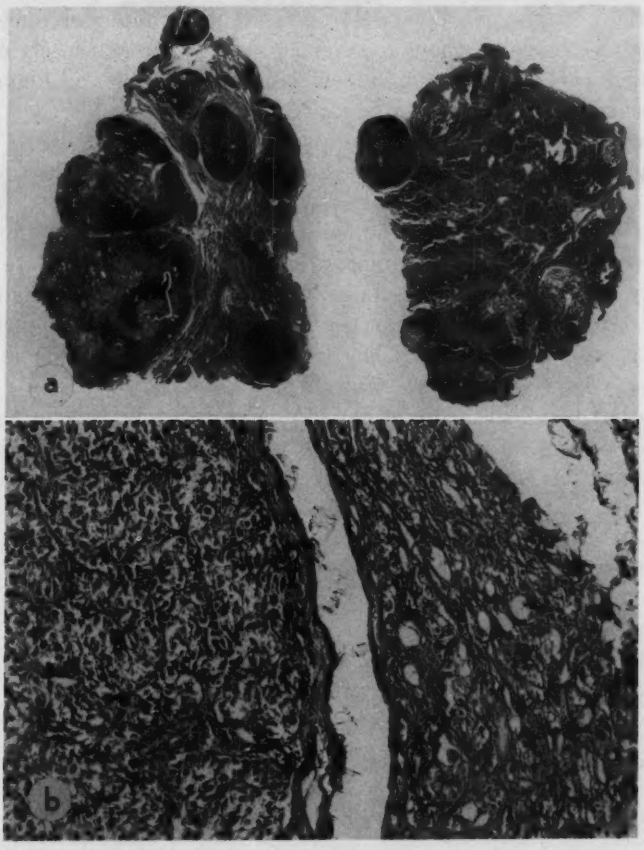

FIG. 4. Goitrous cretinism. **a.** Mounted microscopic section through both lobes of the thyroid showing multiple adenomas (×1½). **b.** Section through margin of one of adenomas shown in **a** (hematoxylin and eosin; ×140).

In every instance, attention was first directed to the disease by the finding of an enlarged, nontender cervical lymph node or a swelling in the thyroid. Enlargement of one or more cervical lymph nodes was the presenting complaint in 36 of the 46 patients. Four of the 36 were noted at the time of the original examination to have bilateral enlargement of cervical lymph nodes due to metastasis. Of clinical importance is the fact that all except 3 of the 36 patients with metastasis to cervical lymph nodes had palpable abnormalities of the thyroid at the time of the original examination. When it is pointed out that the remaining 10 patients of the 46 were prompted to see a physician because of a mass in the thyroid, it becomes evident that 43 of the 46 patients had palpable abnormalities of the thyroid gland.

In most instances, firm, nodular or irregular nontender masses were palpated. Occasionally, the gland was asymmetrical or diffusely enlarged. Two patients complained of mild respiratory obstruction and 1 complained of hoarseness.

The common type of carcinoma arising in the thyroid gland of children is slow-growing papillary and follicular adenocarcinoma, which occurred in 41 of our 46 patients. Histologically, the tumor may be predominantly papillary (Fig. 5*a*) or largely follicular in structure (Fig. 5*b*), or it may exhibit varying degrees of admixture of the two types. In spite of their relatively benign histologic appearance these tumors metastasize to regional lymph nodes early in the course of their development. Less frequently and usually much later, they metastasize to the lungs and occasionally to bones or other structures.

The other histologic type of carcinoma seen in children in this series was the solid or solid and follicular carcinoma. These circumscribed or encapsulated carcinomas are frequently referred to as malignant adenomas (Fig. 5*c*).

The treatment of carcinoma of the thyroid gland in children is surgical in most cases, although radioiodine and roentgen-ray or radium therapy may be of value in some instances.

Seven deaths are known to have occurred in this group. The only infant in the series died of respiratory obstruction soon after operation. The remaining 6 patients died, presumably of carcinoma of the thyroid, twenty-one, twenty, eighteen, eleven, seven and one year after the diagnosis was established. The survival rates are listed in Table 4.

COMMENT

Our experience indicates that there has been a definite change in the incidence of diseases that produce nodular enlargement of the thyroid gland of children. Patients with nodular goiter due to goitrous cretinism and those with congenital goiter are included in this study only for completeness. Goiters due to these conditions are rare and usually present no problem in diagnosis. Teratomas arising in the thyroid may produce nodular enlargement of the thyroid, but we have not observed a child with this condition.

The number of children seen in our practice because of carcinoma of the thyroid and lymphocytic thyroiditis has definitely increased, whereas the number seen because of adenomatous goiter has decreased (Fig. 1).

In recent years lymphocytic thyroiditis has taken a prominent place among the diseases that produce nodular goiter. Although suspected in 1 child in 1924, lymphocytic thyroiditis was not definitely diagnosed in a child seen at the Mayo Clinic until 1937. The cause for the increased number of children being seen with thyroiditis is not known; it seems un-

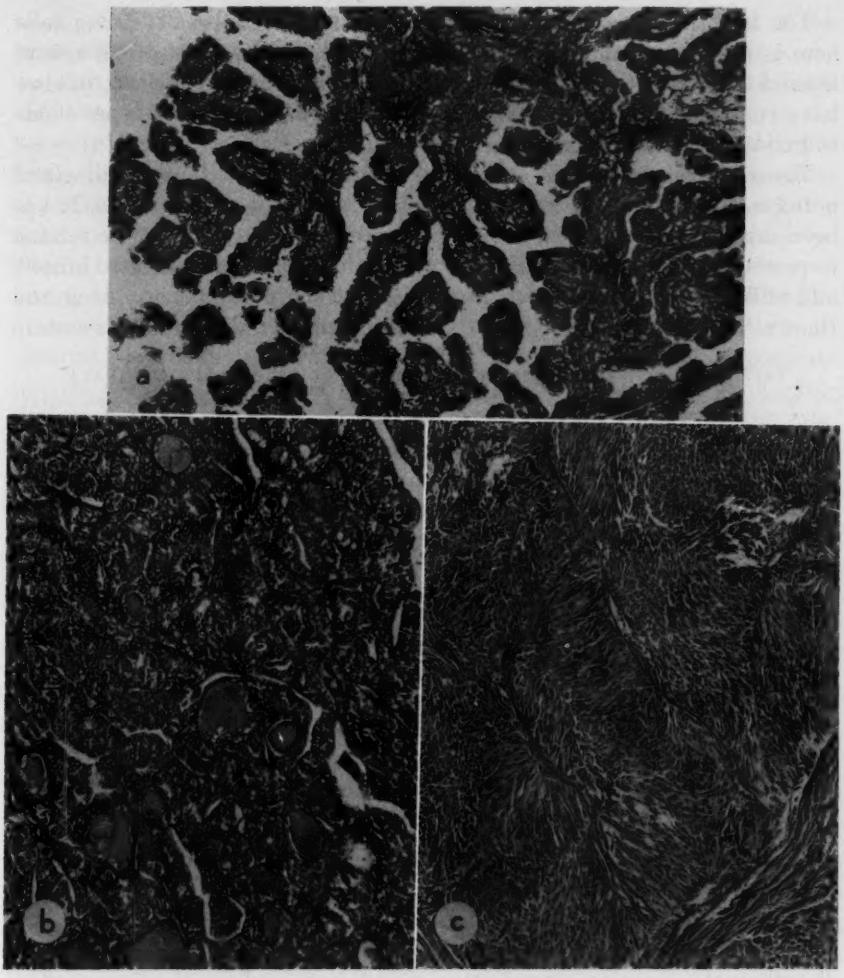

FIG. 5. Carcinoma of the thyroid gland in children. Sections stained with hematoxylin and eosin (×110). **a.** Papillary adenocarcinoma. **b.** Follicular adenocarcinoma. **c.** Solid carcinoma.

likely that the increase could be attributable to frequent failure to detect this type of goiter in the years prior to 1937, since it long has been the practice here to obtain biopsy material from any child with a firm nodular or irregular goiter, if at all possible to do so. There were 34 children with adenomatous goiter who did not have biopsy (Fig. 1), all of whom were seen before 1936. In only 1 of these children, namely the previously mentioned one who was seen in 1924, was the recorded clinical description of the thyroid compatible with a possible diagnosis of thyroiditis.

The fact that fewer children with adenomatous goiters are being seen here is almost certainly due, at least in part, to the widespread use of iodized salt (10). Other factors may be important but the fact that we have continued to see children with nodular goiters of other types tends to exclude the possibility of patient selection.

The relatively increased incidence of carcinoma of the thyroid gland noted in this series is in accord with observations made by others. It has been suggested that the increased incidence of the disease may be related to previous roentgen-ray or radium irradiation (7) administered to infants and children for a variety of diseases about the nasopharynx, neck and thorax. The known carcinogenic effect of ionizing irradiation under certain

TABLE 4. CARCINOMA OF THE THYROID GLAND IN CHILDREN: SURVIVAL DATA*

Period (yrs.)†	Patients		Lived beyond indicated period	
	Total	Traced	Number	Per cent of traced patients
3	32	31	30	96.8
5	24	22	21	95.5
10	18	15	13	86.7
15	14	12	10	83.3
20	8	5	3	60.0

* Inquiry as of January 1, 1955.

† The 3-year group includes only patients treated before 1952, the 5-year group only patients treated before 1950, the 10-year group only patients treated before 1945, and so forth. Hospital deaths are excluded in the calculation of survival rates.

circumstances makes this an attractive suggestion, but proof of its importance is lacking. Many patients with carcinoma of the thyroid give histories of having had irradiation during the years preceding discovery of the carcinoma. On the other hand, not all patients give such a history. Furthermore, previous irradiation could not explain the presence of carcinoma noted at the time of birth, nor would it seem logical as an explanation of the difference in sex distribution.

Although it is impossible to establish true rates of incidence of disease from a study of this type, since many of the patients are referred to the clinic after the diagnosis has been established, it is interesting to note the change in the percentage of children with carcinoma as compared with all children with nodular goiter seen at the clinic during the years 1908 through 1955 (Table 5). Thus, during this period of forty-eight years, carcinoma of the thyroid was the cause of nodular goiter in 35.4 per cent of

all the children with nodular goiter. Early in this period, namely in the years 1908 through 1919, carcinoma accounted for only 4.5 per cent of the nodular goiters, but in succeeding years adenomatous goiter decreased and carcinoma increased so that in the latter part of the period, namely in the years 1950 through 1955, carcinoma accounted for 70 per cent of the children with nodular goiter; this occurred in spite of the fact that the number of patients with thyroiditis increased. Again we wish to point out that these figures do not represent the true incidence of nodular goiter in children. This is best demonstrated by the fact that two thirds of the children seen during the period 1950 through 1955 were referred to the clinic after the diagnosis of carcinoma of the thyroid had been established by biopsy. In contrast, during the years 1940 through 1949, in only 4 of the 11 patients was the diagnosis established before they arrived at the clinic. Such selection of patients tends to give an erroneous impression as to the true incidence of carcinoma. Nonetheless, at the present time about 3 out of 4 children with nodular goiter seen at the Mayo Clinic have carcinoma of the thyroid.

TABLE 5. NODULAR ENLARGEMENT OF THE THYROID GLAND IN INFANTS AND CHILDREN: DISTRIBUTION OF PATIENTS ACCORDING TO NATURE OF LESION AND YEAR OF DIAGNOSIS

Period	Patients with benign nodular goiter					All patients with nodular goiter		
	Adenomatous goiter	Lymphocytic thyroiditis	Goitrous cretinism	Congenital goiter	Total	Total	Carcinoma of thyroid	
							Number	Per cent
1908–1919	18	—	3	—	21	22	1	4.5
1920–1929	32	—	—	—	32	35	3	8.6
1930–1939	10	1	—	2	13	23	10	43.5
1940–1949	4	3	2	—	9	20	11	55.0
1950–1955	4	4	—	1	9	30	21	70.0
Total	68	8	5	3	84	130	46	35.4

SUMMARY AND CONCLUSIONS

Of 130 children with nodular enlargement of the thyroid gland examined at the Mayo Clinic during the years 1908 through 1955, 68 had adenomatous goiter, 46 had carcinoma, 8 had lymphocytic thyroiditis, 5 had goitrous cretinism and 3 had congenital goiter. Thus carcinoma accounted for 35.4 per cent of the patients with nodular goiter. Of greater interest than the percentage of children with carcinoma is the fact that carcinoma and thyroiditis have been seen with much greater frequency during recent years, whereas adenomatous goiter has been seen less frequently. Thus carcinoma of the thyroid was observed in only 1 child during the years 1908 through 1919 and accounted for only 4.5 per cent of the cases of nodular goiter in children. During the period 1950 through 1955, however, carcinoma was present in 70 per cent of the children with nodular goiter.

Since the nature of the disease that is producing nodular enlargement of the thyroid gland in a child cannot, in most instances, be determined except by histologic study, we prefer surgical treatment, not only to obtain a biopsy specimen but also for removal of the goiter. At present we advise surgical treatment for all children with nodular goiter except those with the congenital type, and we advise careful observation of these patients to see that the goiter disappears with medical management.

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BIOLOGIC ACTIVITY OF PORK AND BEEF THYROID PREPARATIONS*

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THE United States Pharmacopeia description of Thyroid has remained essentially unchanged since the Ninth Revision became effective in 1916. According to the recent Fifteenth Revision, U.S.P. Thyroid is "obtained from domesticated animals that are used for food by man" and is standardized as containing "not less than 0.17 per cent and not more than 0.23 per cent of iodine (I) in thyroid combination. . . ." It is also stated that "A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose" and other diluents. According to this description, the fresh or processed glands of swine, cattle or sheep might be used alternatively or blended together to meet the U.S.P. requirements.

Actually, swine thyroids are the glands most commonly processed commercially in the United States (1) because of their higher iodine content, greater ease of removal from the carcass, and handling characteristics in desiccation or extraction procedures as compared with bovine glands. The supply of pork thyroids may fluctuate considerably, however, depending upon normal seasonal variations and, particularly, economic conditions. In other countries or regions of the world, cattle (or sheep) raised in larger numbers may be the most practical source of the glands. For these reasons it was desirable to compare the biologic activities of beef and pork thyroid preparations, foreign and domestic. The evidence presented here demonstrates a significant difference in activity in the rat between these two sources when administered on any common basis of dosage.

MATERIALS AND METHODS

Antigoitrogenic assay

In each assay, female albino rats weighing 160–190 Gm. at the start, were grouped and given the assay diets and plain tap water without restriction according to the following design:

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This article will be included in the bound volume of the 1956 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available early in 1957.

16 rats: powdered Rockland stock diet containing a low dosage of Standard (S_1) and 0.3 per cent thiouracil.
16 rats: powdered stock diet containing a high dosage of Standard ($S_2 = 1.5 \times S_1$) and 0.3 per cent thiouracil.
16 rats: powdered stock diet containing a low dosage of Unknown (U_1) and 0.3 per cent thiouracil.
16 rats: powdered stock diet containing a high dosage of Unknown ($U_2 = 1.5 \times U_1$) and 0.3 per cent thiouracil.
8 rats: plain powdered stock diet (normal controls).
8 rats: powdered diet containing 0.3 per cent thiouracil (thiouracil controls).

This unit design had to be replicated using higher dosage levels for the beef preparations, *i.e.*, U_3, U_4 and U_5, because these materials induced low responses at dosage levels equal to that of the standard. The weights of standard and unknown blended into the diet were based on the total iodine analysis of each preparation and dosages were calculated in terms of micrograms of thyroid total iodine per 100 grams of diet.

Animals were housed (4 per cage) in quarters maintained at 74° ± 3° F., and no special care, other than replenishing each cage with water and the proper diet, was required during the assay period. At the end of fourteen full days, the experimental and control groups were sacrificed. The thyroids were dissected, weighed to the nearest 0.1 mg. and recorded as mg. of gland weight per 100 Gm. of body weight.

Calorigenic assay

The method employed was essentially the same as that previously reported by Kroc *et al.* (2). Two to three weeks before the basal metabolic rate (BMR) tests, ground Rockland rat diet was started in male rats weighing 280–320 Gm. The daily five-hour afternoon feeding, nineteen-hour fasting schedule employed by Barker (3) was followed for the two-week to three-week conditioning period and for the succeeding five days when daily BMR tests were run. The rats were placed in metabolic chambers in the morning, thirty minutes before oxygen consumption readings were made at ten-minute intervals, from sixteen hours to seventeen and a half hours after food was made unavailable in a specially designed cage. Twelve metabolism chambers were housed in a constant-temperature, forced-air circulation cabinet maintained at 29° ± 0.5° C. Closed-circuit units of the Benedict (4) type were used. The 4 lowest of 6 ten-minute O_2 consumption readings for each rat were averaged, corrected to standard temperature and pressure, and calculated on a body-weight basis, to obtain the "basal" rate for that day. The rates for the first two days were averaged to obtain the pre-treatment BMR level. Preparations were administered orally (stomach tube) once daily for three days after the rats were removed from the chambers on the second to fourth days and before food was made available. The BMR on the fifth day—approximately seventy hours and twenty-two hours, respectively, after the first and last doses—was taken as the post-treatment rate for comparison with the pre-treatment BMR.

Statistical methods

The foregoing assays were planned to fulfill the requirements of either a "four-point or six-point balanced design." The completed assays were analyzable by the methods of Bliss and Marks (5), Irwin (6) and Bliss (7). Each assay was subjected to an analysis of variance from which the error term "s" for the degrees of freedom within groups was obtained. Least-squares analysis of dose-response for standard and unknown yielded a common slope "b." The index of precision (lambda, λ, or s/b) was calculated for com-

parison between assays. All calculations were on the basis of log-dose versus linear response.

In the initial assay of each unknown, the dosage levels were based on the assumption that there was no difference in biologic potency per unit of thyroid total iodine; therefore, they were identical in most cases with the levels of the standard. However, with the beef preparations, repetition of the assays at higher dosage levels was necessary in order to induce responses similar to those observed for the standard. Thus, although the "null-hypothesis" was rejected on the basis of the initial assay of each beef preparation, the standard error of the potency ratio was larger than average, due to the discrepancy in the mean responses for standard and unknown. The second assay at higher dosage levels for the unknowns reduced the mean differences and consequently the standard error of the potency estimate was also reduced to the expected level.

Preparations

All of the 11 thyroglobulin samples listed in Table 1 were made by the same procedure, but those of foreign origin were from glands collected and processed in Argentina. The thyroglobulin extracts were prepared by saline extraction and centrifugation and filtration to remove cells, connective tissue and most of the fat. Proteins were then precipitated from the supernatant solution by heating and acidification. Finally, adsorbed fats and combined lipids were removed by repeated solvent extraction of the precipitate, which was then dried, ground and sieved to a fine powder.

One of the 3 desiccated beef thyroid preparations, No. 6249, was of the same foreign origin as the beef thyroglobulins. The other 2 were domestic preparations purchased for this study. Preparation No. 87104 was an experimental lot[1] with an iodine content of 0.44 per cent which, when corrected for residual lipid content, approximated 0.54 per cent. With this correction, all of the preparations may be compared for their total and "thyroxine" iodine contents, because analyses for residual moisture and lipids (alcohol extractives) showed these factors to be uniformly low (less than 5 per cent and 2.6 per cent respectively).

Beef thyroid No. N2602 was a marketed product and was obtained from a local pharmacy. According to descriptive literature, it was prepared by a low-temperature desiccation and lipid extraction process, and was labelled as a "bovine thyroid preparation, containing organically bound iodine equivalent to U.S.P. thyroid." Whereas the iodine analysis of 0.56 per cent shown in the table is based on a sample freed from diluents, the tablets on an "as is" basis assayed 0.20 per cent iodine as indicated by the label. All the other preparations were in the form of concentrates without added diluents.

Two reference standard pork thyroglobulins were used in the course of these bioassays. No. 06985 was employed in later tests when the supply of No. 5640 was nearly exhausted after many years of use. However, prior to the adoption of the new standard, complete antigoitrogenic and calorigenic assays showed that it possessed standard activity.

RESULTS AND DISCUSSION

Results of *antigoitrogenic assay of the 2 standard pork thyroglobulins versus 5 different beef preparations* are listed in Table 2. Values for the unknowns ranged from 40 to 63 per cent of the standard per unit of total iodine

[1] Obtained through the courtesy of Dr. David Klein, Wilson Laboratories, Chicago, Ill.

TABLE 1. CHEMICAL ANALYSES OF PREPARATIONS USED

Preparations	Total* iodine (%)	"Thyroxine† iodine" (%)	Ratio, $\frac{\text{thyroxine I}}{\text{total I}}$
Standard pork thyroglobulins:			
S #5640	0.84	0.30	0.36
S #06985	0.86	0.28	0.33
Beef thyroglobulins:			
Foreign #6223	0.62	0.21	0.34
Foreign #288	0.62	0.22	0.35
Beef desiccated thyroid:			
Foreign #6249	0.45	0.17	0.38
Domestic #N2606‡	0.56	0.17	0.30
Domestic #87104	0.44	0.14	0.32
Foreign pork thyroglobulins:			
#5707	0.99	0.36	0.36
#6236	0.98	0.33	0.34
#284	0.88	0.32	0.36
#7401	0.93	0.39	0.41
Domestic pork thyroglobulins:			
#11064	0.82	0.28	0.34
#15164	0.85	0.27	0.32
#19924	0.84	0.29	0.35
#12495	0.87	0.33	0.38
#19785	0.85	0.28	0.33

* U.S.P. XIV.

† Analytical method of Blau (1935).

‡ A commercial preparation: analyses based on sample freed from diluents.

dosage. The difference in each assay was subjected to "Student's *t*-test" and all were highly significant at the 99 per cent confidence limit, $P < 0.01$. Instead of depicting the observed means (Table 2), the expected responses at each of the two dosage levels of standard and unknown were calculated from the regression equations and combined slope for each assay. The two sets of points for each assay were connected with straight lines. Thus, Figure 1 shows paired parallel lines with corresponding numbers for each self-contained assay, and the potency ratio may be estimated by noting the dosages required for any level of response.

One of the beef preparations, No. 87104, was assayed *calorigenically* according to a balanced design (Fig. 3, Table 4). As observed in the goiter

TABLE 2. ANTIGOITROGENIC ASSAYS OF STANDARD (S) PORK THYROGLOBULINS VERSUS FOREIGN AND DOMESTIC BEEF THRYOID PREPARATIONS (U)
(16 rats at each of two dosage levels)

Preparations	Dosage*	Response†	(−)b	s	Lambda	Relative potency of unknown	P = 0.95	
							Range of potency	Limits of error
Pork thyroglobulin S, #5640	45.0	14.3±1.4‡						
	67.5	8.0±1.3						
			41.2	4.942	0.120	45%	39–52%	87–115%
Beef thyroglobulin, foreign, #6223	101.3	15.1±1.9						
	151.9	6.9±0.6						
Pork thyroglobulin S, #5640	45.0	16.8±1.4						
	67.5	9.1±1.2						
			41.7	5.358	0.128	63%	55–72%	87–115%
Beef thyroglobulin, foreign, #288	67.5	17.4±1.4						
	101.3	10.4±1.3						
Pork thyroglobulin S, #5640	45.0	19.3±1.4						
	67.5	12.8±1.6						
			28.1	5.289	0.186	46%	37–57%	81–124%
Beef, desiccated, domestic, #N2606	91.1	18.6±1.0						
	136.6	15.2±1.4						
Pork thyroglobulin S, #06985	55.0	15.4±1.4						
	82.5	7.6±1.0						
			43.7	4.340	0.099	40%	36–45%	89–112%
Beef, desiccated, foreign, #6249	123.8	13.5±1.3						
	185.6	5.9±0.2						
Pork thyroglobulin S, #06985	50.0	14.5±1.1						
	75.0	5.4±0.5						
			44.7	3.450	0.077	42%	39–46%	92–109%
Beef, desiccated, domestic, #87104	118.9	13.1±1.0						
	178.4	6.5±0.6						

* Micrograms thyroid iodine per 100 grams of diet for fourteen days.
† Average thyroid weight: mg./100 Gm. body weight.
‡ Standard error of the mean.

prevention assay, this material was about 40 per cent as active as the pork reference standard. Although this difference was highly significant ($P < 0.01$), it should be noted that the error of this assay approximated *minus* 33 per cent to *plus* 50 per cent of the potency estimate. By contrast, the precision observed in our antigoitrogenic assays in general was about ±15 per cent for a given potency estimate (see "Limits of error," Tables 2 and 3) when approximately the same number of rats were used in either assay. Three of the remaining beef preparations were also tested calorigenically at one or more dosage levels (Table 4). Foreign preparations No. 6223 and No. 6249, tested at one and two dosage levels respectively, were not significantly less potent ($P > 0.05$) than standard, even though the results indicated the possibility of lower potency for these materials. The domestic preparations (No. N2606 and No. 87104), however, were each significantly less potent ($P < 0.01$) than the standard pork thyroglobulins.

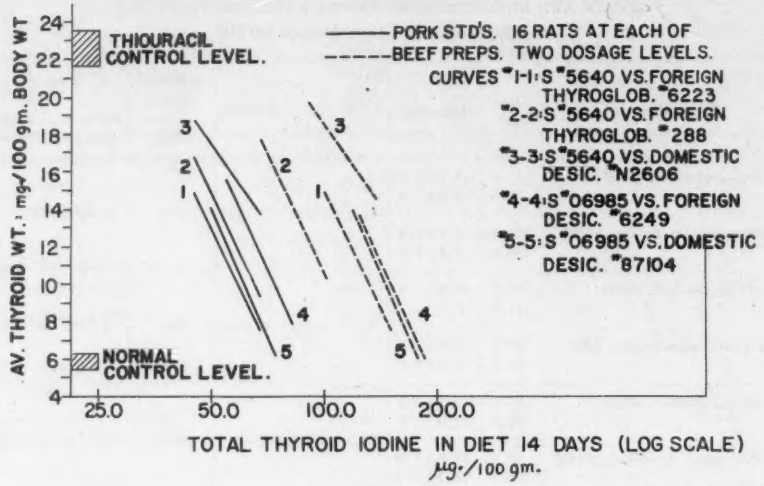
THIOURACIL CONTROL LEVEL.
NORMAL CONTROL LEVEL.
PORK STD'S. 16 RATS AT EACH OF
BEEF PREPS. TWO DOSAGE LEVELS.
CURVES 1-1, S 5640 VS. FOREIGN THYROGLOB. 6223
2-2, S 5640 VS. FOREIGN THYROGLOB. 288
3-3, S 5640 VS. DOMESTIC DESIC. N2606
4-4, S 06985 VS. FOREIGN DESIC. 6249
5-5, S 06985 VS. DOMESTIC DESIC. 87104
AV. THYROID WT.: mg./100 gm. BODY WT
TOTAL THYROID IODINE IN DIET 14 DAYS (LOG SCALE)
μg./100 gm.

FIG. 1. Antigoitrogenic assays of standard pork thyroglobulins versus foreign and domestic beef thyroid preparations. The dose-response curves were calculated from the assays listed in Table 2.

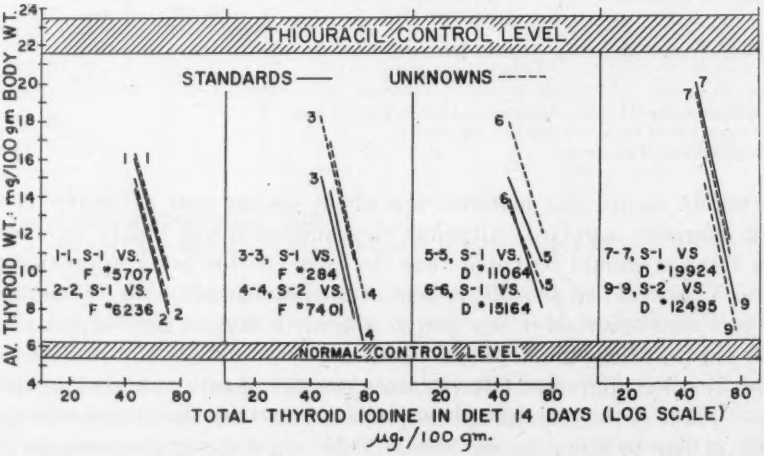
THIOURACIL CONTROL LEVEL
STANDARDS
UNKNOWNS
1-1, S-1 VS. F 5707
2-2, S-1 VS. F 6236
3-3, S-1 VS. F 284
4-4, S-2 VS. F 7401
5-5, S-1 VS. D 11064
6-6, S-1 VS. D 15164
7-7, S-1 VS D 19924
9-9, S-2 VS. D 12495
NORMAL CONTROL LEVEL
AV. THYROID WT.: mg/100 gm BODY WT.
TOTAL THYROID IODINE IN DIET 14 DAYS (LOG SCALE)
μg./100 gm.

FIG. 2. Antigoitrogenic assays of standard (S-1, No. 5640 and S-2, No. 06985) pork thyroglobulins versus foreign and domestic pork thyroglobulin preparations. The dose-response curves were calculated from the assays listed in Table 3.

TABLE 3. ANTIGOITROGENIC ASSAYS OF STANDARD (S) PORK THYROGLOBULINS VERSUS FOREIGN AND DOMESTIC PORK THYROGLOBULIN PREPARATIONS (U)
(16 rats at each of two dosage levels per preparation)

Preparations	Dosage*	Response†	(−)b	s	Lambda	Relative potency of unknown	P=0.95	
							Range of potency	Limits of error
Pork thyroglobulin S, #5640	45.0	15.5±1.5‡	34.9	4.763	0.136	98%	83–116%	85–118%
	67.5	10.1±1.1						
Pork thyroglobulin, foreign, #5707	45.0	16.5±1.1						
	67.5	9.6±1.3						
Pork thyroglobulin S, #5640	45.0	14.3±1.3	36.6	3.799	0.104	97%	86–110%	89–113%
	67.5	8.0±0.8						
Pork thyroglobulin, foreign, #6236	45.0	14.9±0.7						
	67.5	8.3±0.8						
Pork thyroglobulin S, #5640	45.0	15.2±1.1	42.6	4.697	0.111	84%	73–97%	87–115%
	67.5	7.5±1.0						
Pork thyroglobulin, foreign, #284	45.0	18.2±1.1						
	67.5	10.9±1.4						
Pork thyroglobulin S, #06985	50.0	14.2±1.2	44.9	4.210	0.094	89%	79–100%	89–112%
	75.0	6.7±1.1						
Pork thyroglobulin, foreign, #7401	50.0	16.8±0.8						
	75.0	8.5±1.1						
Pork thyroglobulin S, #5640	45.0	15.5±1.5	23.8	4.606	0.193	115%	90–147%	78–128%
	67.5	10.1±1.1						
Pork thyroglobulin, domestic, #11064	45.0	12.9±0.9						
	67.5	9.9±1.3						
Pork thyroglobulin S, #5640	45.0	14.4±1.0	32.7	4.660	0.143	74%	61–90%	82–122%
	67.5	7.5±1.1						
Pork thyroglobulin, domestic, #15164	45.0	17.5±1.4						
	67.5	12.9±1.2						
Pork thyroglobulin S, #5640	45.0	20.3±1.4	48.0	6.332	0.132	103%	89–119%	86–116%
	67.5	11.3±2.0						
Pork thyroglobulin, domestic, #19924	45.0	19.2±1.3						
	67.5	11.3±1.6						
Pork thyroglobulin S, #5640	50.0	17.3±1.4	41.2	4.970	0.121	86%	74–100%	86–116%
	75.0	9.0±1.2						
Pork thyroglobulin S, #06985	50.0	19.0±0.8						
	75.0	12.8±1.5						
Pork thyroglobulin S, #06985	50.0	17.2±1.5	45.0	4.720	0.105	107%	95–120%	89–112%
	75.0	7.1±0.9						
Pork thyroglobulin, domestic, #12495	50.0	14.2±1.0						
	75.0	7.4±1.1						
Pork thyroglobulin S, #06985	50.0	17.2±1.4	58.3	4.510	0.077	97%	89–106%	92–109%
	75.0	7.3±0.9						
Pork thyroglobulin, domestic, #19785	49.4	18.7±1.1						
	74.1	8.0±1.0						

* Micrograms of thyroid iodine per 100 Gm. of diet for 14 days.
† Average thyroid weight—mg./100 Gm. of body wt.
‡ Standard error of the mean.

When the data of the foregoing antigoitrogenic and BMR assays were calculated in terms of "thyroxine" iodine, the relative potencies of beef preparations were nearly identical to those listed in Table 2. This was expected because of the close similarity of the "thyroxine" iodine to total iodine ratios for the preparations from both species (Table 1). Roche and

Michel (8), using a different method of analysis, reported similar ratios for normal mammalian thyroids of many species.

Table 3 and Figure 2 show the results of 10 *antigoitrogenic assays of foreign and domestic pork thyroglobulins versus our standard pork preparations*. From inspection of the relative potency and confidence limit columns of Table 3 it may be seen that all but 2 of the preparations had standard activity per unit of total or "thyroxine-iodine" content. The 2 which

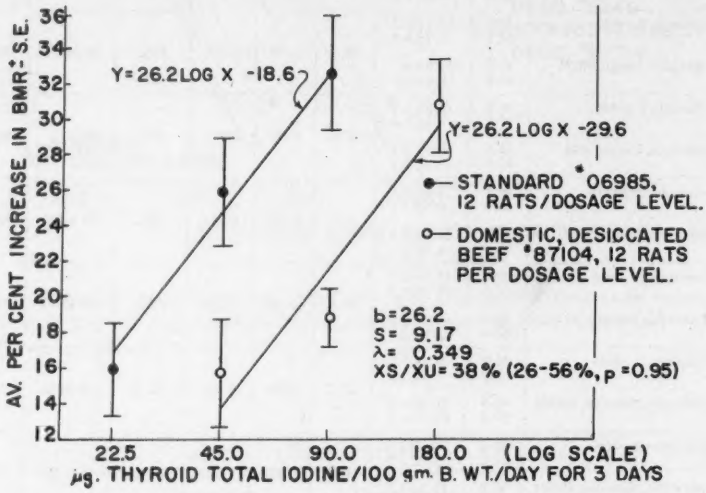

FIG. 3. Calorigenic assay of standard pork thyroglobulin versus domestic, desiccated beef thyroid given orally by gavage. The combined assay slope was used to calculate the regression equations shown.

differed significantly were each less potent than the standard. Thus, for No. 284 the difference was significant at the 95 per cent but not at the 99 per cent confidence limit ($P<0.05>0.01$); for No. 15164 the difference was significant at the higher confidence level ($P<0.01$). However, the relative potencies of these 2 preparations (84 and 74 per cent of standard, respectively) were above the potencies observed for the 5 beef materials. Four of these assayed 40–46 per cent and 1 assayed 63 per cent of the standard, as described earlier in this communication. These results indicate the value of routine bioassays of thyroid preparations against a standard of similar nature (2), regardless of the species used as a source of glands, in order to detect unsuspected variations in potency.

The *goiter-prevention assay method* of Dempsey and Astwood (9) has been used extensively, and primarily for exploring the activities of parenterally administered compounds. Relatively few studies—*e.g.*, those of Monroe

TABLE 4. CALORIGENIC ASSAYS OF STANDARD PORK THYROGLOBULINS VERSUS FOREIGN AND DOMESTIC BEEF THYROID PREPARATIONS

Preparations	No. of rats	Dosage*	Response†	Relative potency of unknown	P=0.95	
					Range of potency	Limits of error
Standard No. 5640	16	90.0	21.6±2.3	—	—	—
Foreign thyroglobulin No. 6223	16	90.0	19.3±1.7	—	—	—
Standard No. 5640	32	90.0	20.1±1.5			
	32	270.0	31.8±2.1			
				48%	37–62%	77–129%
Domestic desiccated,	12	54.0	5.8±1.3			
No. N2606	34	162.0	16.5±1.4			
	33	486.0	31.9±1.6			
Standard No. 06985	18	90.0	16.9±2.6			
	18	270.0	21.8±2.0			
				62%	37–105%	60–169%
Foreign desiccated,	18	90.0	6.9±1.4			
No. 6249	18	270.0	22.7±2.9			
Standard No. 06985	12	22.5	15.9±2.6			
	12	45.0	25.8±3.0			
	12	90.0	32.5±3.2			
				38%	26–56%	68–147%
Domestic desiccated,	12	45.0	15.7±2.6			
No. 87104	12	90.0	18.6±1.4			
	12	180.0	30.7±2.6			

* Micrograms thyroid iodine per 100 grams body wt. per day, for 3 days, by gavage.
† Average percentile increase in BMR ± S.E. for observations recorded approximately 24 hours after the last dose.

and Turner (10), Herrold *et al.* (11) and Ferguson and Warson (12)—have involved oral administration by blending the relatively insoluble compounds or thyroid preparations in the diet. The latter method has the advantage of convenience and practicality over parenteral injections or oral gavage. Ferguson and Warson (12) using the goiter-prevention method for assaying thyroidal materials (including "dried" thyroid) in the diet, reported a value of 0.2 as the index of precision for calculation of the minimum statistical error of their relative potency estimates. Our average lambda, (s/b) for the 15 assays in this report was 0.12 (Tables 2 and 3; Figs. 1 and 2). Our highest individual estimate of precision was less than

0.2. It is evident, therefore, that under actual working conditions the method followed here attains a relatively high degree of precision. The task of comparing results between laboratories would be greatly facilitated by a simplified, standardized procedure of antigoitrogenic assay (including standard methods of statistical design and analysis), such as those we have reported.

The standardized goiter-prevention method which we employed demonstrated that the lower potency of the beef preparations was independent of total iodine, "thyroxine-iodine," methods of processing and geographic origin. The question arises as to whether variations in the amounts of 3,5,3′-triiodothyronine and other active compounds may account for the difference in potency. To our knowledge, there has not been sufficient quantitation of the compounds in these two species to explain the potency difference. Regardless of the ultimate explanation, it is apparent that beef preparations diluted to conform with U.S.P. specifications for total iodine or with the British Pharmacopeia for "iodine in thyroxine combination" would still exhibit (in the rat) only half the activity of the standard pork preparations diluted to the same respective iodine concentrations. Independently, and during the course of these experiments, Howland (13) observed that hypothyroid patients required dosages in the ratio of 2 or 3 to 1 for an experimental beef thyroid preparation and a pork thyroglobulin product, respectively. Both preparations were of U.S.P. total iodine content. That species variation may exist was indicated in 1935 by Thompson *et al.* (14), who compared maintenance doses in the same myxedematous patient and found that certain lots of sheep and beef thyroid had less effect than a lot of hog thyroid in doses containing the same total amounts of iodine. However, two years earlier, in studies on 2 patients with myxedema, Thompson *et al.* (15) compared a specific lot of sheep thyroid (Wilson) containing 0.056 per cent iodine with commercial hog thyroid (Wilson) containing 0.23 per cent iodine and found that they had approximately equal effects on the basal metabolism, when considered on the basis of equivalent total iodine content. Parkes' data (16) showed that pig thyroids were more active than those of the ox, sheep or horse per unit amount of total or "thyroxine iodine" by the *Xenopus* tadpole test. Further clinical studies with well standardized preparations are necessary in order to obtain a definitive clinical assay of products of both species. It is also apparent that animal and clinical experiments with thyroid preparations from other species are desirable.

SUMMARY

Antigoitrogenic assays and supporting calorigenic tests have consistently shown significantly lower potencies ($P < 0.01$) for preparations processed from cattle thyroids than those made from swine thyroids.

Regardless of geographic origin or method of preparation, 4 of 5 beef preparations showed 40 to 46 per cent and 1 showed 63 per cent of the potency of pork thyroglobulin reference standards on the basis of either total or "thyroxine" iodine. It is evident that if these beef preparations were diluted to meet U.S.P. or B.P. specifications for thyroid, they would still exhibit only half the biologic potency of pork preparations comparably diluted.

Eight of the 10 pork preparations assayed were not significantly different from the standard. Two were significantly lower in potency—one, 74 per cent ($P < 0.01$), and the other 84 per cent ($P < 0.05, > 0.01$). These observations demonstrate the importance of biologic standardization of thyroid preparations.

Quantitative biochemical characterization of thyroid preparations from swine and cattle would be desirable and might provide evidence to account for the potency differences. The thyroids of other species such as sheep also should be investigated for their biochemical and biologic properties.

This study demonstrates the usefulness of a statistically designed bioassay method, such as the antigoitrogenic method described, for assessing the activity of experimental and commercial thyroid products.

Acknowledgments

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SPINAL CORD LESION WITH HYPOGONADISM AND GYNECOMASTIA; CHROMOSOMAL SEX

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TESTICULAR atrophy accompanied by hypogonadism and at times by gynecomastia, has been observed to develop following traumatic transection of the spinal cord. Detailed reports, some featuring hormonal assays and testicular biopsies, have been published previously (1–6). The possibility of a neurogenic cause of the hypogonadal syndrome in such cases has been suggested (1, 3, 4). Hypogonadism has been seen occasionally in cases of degenerative disease of the central nervous system (7–9) and here, too, a neurogenic mechanism has been mentioned, although adequate information is not furnished in most of these reports. It is the purpose of this report to present a case of hypogonadism accompanied by gynecomastia in a man with a diffuse lesion of the central nervous system, including some of the hormonal and histologic studies which might help in elucidating the pathogenesis. Furthermore, an attempt has been made to determine the chromosomal sex, in view of the intersex hypotheses of gynecomastia.

CASE HISTORY

The patient was a 36-year-old veteran of Polish parentage. Nothing could be learned about the parents' families except that they lived in adjacent villages in the old country. Consanguinity was denied.

He was physically and mentally well until the age of about 23. He enlisted in the Army and was accepted as a medical student under the ASTP program. He began experiencing unexplained tremors and weakness in the right leg at age 23. At the onset, because of indefinite symptoms and signs, the diagnosis was conversion reaction. Six months later, he was admitted to a State hospital because of peculiar and impulsive behavior. Soon he showed signs of marked psychotic regression and was given a course of electroshock therapy. After eighteen months' stay in the State hospital, he was transferred to the VA Hospital, Canandaigua, N. Y. (1947) with a diagnosis of dementia praecox, catatonic type. This diagnosis corresponded well with the patient's behavior at the time.

On physical examination, left pes cavus was discovered; otherwise, physical and neurologic findings were negative. The patient's condition deteriorated rapidly, and within a short time (1948) he was confined to a wheelchair and was incontinent of urine and feces. He manifested marked ataxia and spasticity of the lower extremities, scissor gait,

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sustained bilateral clonus, and bilateral Babinski and Hoffman signs. It was felt that in the differential diagnosis Friedreich's ataxia, familial spastic paraplegia, and multiple sclerosis should be considered. The mental deterioration was thought to be an expression of the organic pathologic condition. From 1952 on, the patient has been apathetic, inarticulate and has required maximum nursing care. In 1953 marked ataxia of the upper extremities was noted and contractures of the lower extremities became intractable. Neurologic findings have since been reviewed, and advanced multiple sclerosis is now considered the most likely diagnosis.

Shortly after the development of the patient's neurologic symptoms, enlargement and fullness of the right breast was noted.

In March 1954 a biopsy specimen was taken from the left testis. (Both testes were small, but the left one appeared to be definitely atrophic.) Biopsy specimens from the right breast and the skin were obtained in June 1954. Hormonal assays were carried out at that time.

Laboratory data

In July 1951 liver function tests revealed 4 plus cephalin flocculation and 8.5 units of thymol turbidity. In March 1954 numerous liver function tests yielded negative results except for slightly prolonged prothrombin time. Hormonal assays were as follows: 24-hour urinary excretion of 17-ketosteroids, 6.9 mg.; of corticoids, 0.76 mg.; of estrogens, 30.4 gamma; and of prolan A, less than 50 mouse units (10). A Thorn test was performed; the initial eosinophil count was 125 per cu. mm., and there was a drop to 40 eosinophils per cu. mm. in four hours.

Histologic findings

Right breast: The section showed a marked increase in connective tissue, which in general was dense and hyaline but loosely arranged in periductal areas. These areas contained a small number of lymphocytes, plasma cells and mononuclear cells. The ducts were not greatly increased in number. Some ducts showed elongation. The lining epithelium of the ducts consisted of one or two layers of epithelial cells which varied from high to low-columnar. Vacuoles were noticed in some epithelial cells. Some ducts showed papillary projections into the lumina. A few lumina contained desquamated epithelial cells.

Left testis (Fig. 1): The section showed testicular tubules which were imbedded in a very loose edematous stroma. The tubule walls were of normal thickness and there were no signs of fibrosis. Some of the Sertoli cells were vacuolated. The germinal epithelium was greatly reduced in amount, and in most instances was composed of poorly differentiated cell types. No mature spermatozoa were found. There was almost complete absence of Leydig cells in the stroma. Blood vessels were sparse, and some hyalinization of the walls was evident.

DETERMINATION OF THE CHROMOSOMAL SEX

A hypothesis suggesting localized cellular differences as a possible cause of gynecomastia has been derived from Goldschmidt's chromosomal intersex theory (11). According to this theory, sex is determined by the balance of male and female factors dependent on the chromosomal equipment of the individual's cells. Thus gynecomastia would be one of the manifestations of an intersexual chromosomal constitution of all the cells of the body.

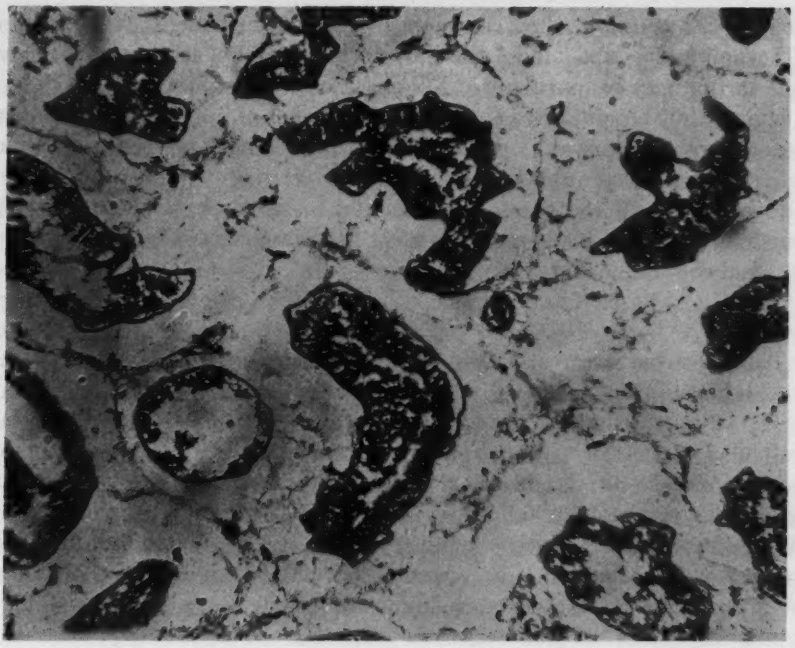

FIG. 1. Section from biopsy specimen of testis, showing intact tubules imbedded in a stroma of loose edematous connective tissue. Tubular lumina contain poorly differentiated germinal cells.

However, hypothetically, one could also visualize the occurrence of an isolated cluster of cells with female chromosomes in an otherwise normal male individual as a result of a developmental aberration (gynandromorphism). This hypothesis has been found attractive by Bauer (12).

A rapid method of determination of the XY and XX chromosomes in somatic cells has been developed (13, 14). It has been found that the nuclei in females contain a special mass of chromatin, the "sex chromatin," which is rarely seen in males. It is suggested that the "sex chromatin" of females is derived from a fusion of portions of the two X chromosomes. Thux, the presence of "sex chromatin" indicates XX cells, without giving any information as to the integrity of the autosomes. This method has been employed in the study of hermaphrodites (13) and transvestites (15). We are greatly indebted to Dr. Murray L. Barr, Professor of Microscopic Anatomy at the University of Western Ontario for performing the test of chromosomal sex in our patient. Skin biopsy specimens were taken from the pectoral region on both sides and from the breast. The epidermal nuclei on both sides manifested typical male morphology. Dr. Barr's

opinion was as follows: "Since the nuclei in these specimens are like those of normal males, and unlike those of normal females, it may be inferred that this patient bears the male XY chromosome complex."

It may thus be concluded that the development of breast enlargement in our case was not caused by an aberration of the X chromosomes determinable by the method applied.

It is of interest that cases of congenital testicular hypoplasia showing female-type nuclei in somatic cells have been found recently (M. L. Barr, personal communication).

DISCUSSION

The endocrine assays appeared to be consistent with the clinical state of gonadal insufficiency.

The histologic findings showed clearly that the tubules in the biopsied testicular segment were not capable of producing mature and functioning spermatozoa. A similar histologic picture has been observed in various syndromes of testicular failure of undetermined etiology in which hypophyseal insufficiency can be excluded as the etiologic factor (16–20). This would be consistent with a congenital structural immaturity, although debilitating nonspecific states are known to bring about a similar histologic type of compromised gametogenesis (19).

It is known that testicular biopsies in paraplegics have revealed germinal deficiency, interpreted as maturation arrest (6) or atrophy of germinal epithelium (3, 4).

Testicular atrophy in cases of post-traumatic paraplegia is interpreted as attributable to severance of a spinal pathway. Thus, the structural and endocrine changes characterizing testicular failure occurring in various syndromes of unknown origin are essentially indistinguishable from the corresponding features of the failure following traumatic transsection of the spinal cord. A possibility suggests itself that even in the non-traumatic syndromes, testicular failure may be caused by lesions of the spinal cord.

This suggestion of a neural mechanism is based, furthermore, on certain experimental data. For example, experimental lesions of circumscribed areas of the hypothalamus (in most instances, of the tuber cinereum) have been repeatedly followed by gonadal disturbance or atrophy (21–26). This gonadal atrophy is thought by some to be caused by severance of a pathway leading from the hypothalamus through the spinal cord to the gonads. Another interpretation is offered in terms of interference with hormonal mediation by the anterior lobe of the pituitary gland.

Up to the present, no specific pathways have been identified as the conductors of the stimuli in the central nervous system, which ultimately

connect with pathways mediating gonadal function. Recently Laruelle (27) described a paraependymal tract that is regarded by Krucke (28) as a possible connecting link between the cerebral and lumbar centers for the sex organs. Such a connection was originally postulated by Goltz (29).

Only scattered clinical observations of hypogonadism in neurologic conditions were found in literature. Complete atrophy of the seminiferous tubules subsequent to invasion of the hypothalamus by a tumor was observed by Cleghorn *et al.* (30). Cases of multiple sclerosis with concomitant testicular atrophy were described by Greene (8). On several occasions hypogonadism or gynecomastia was observed in patients affected with a heredo-familial myelopathy mainly of the Friedreich type (7, 31, 32). Impotence as a postencephalitic development was observed by Cahane and Cahane (33), who concluded that this is further evidence of a diencephalic center regulating genital function. A similar disturbance was noted in males with diabetic neuropathy (9). Kuhnke (34), in a discussion of the causes of the epidemic incidence of gynecomastia which was observed in Germany in the immediate post-war period (34, 35), suggested psychic trauma as a possible factor. He speculated that hypogonadism could be determined psychologically via the mesencephalic-hypophyseal axis. He then quoted, as further corroboration of this concept, a case in which gynecomastia was cured by talks with a "nature healer," thus assuming a reverse effect by a similar pathway. It may be of interest that at one time hypogonadism and gynecomastia were considered to be signs revealing progressive heredo-degeneration ("folie hereditaire"). The case reports of Liegeois (36), Laurent (37) and Magnan (38) reflect this orientation.

Although evidence is scanty and tenuous, a causative connection between hypogonadism and spinal cord disease appears possible. Significantly, Wheeler and associates (39), in classifying gynecomastia, listed that due to transverse myelitis and "other diseases of the spinal cord." Coincidence without causative correlation has not been excluded in any group of the observed cases. Nevertheless, the development of germinal atrophy in paraplegics is suggestive of direct neural involvement.

It should be emphasized that certain syndromes of hypogonadism may well be of genetic origin. Thus, in some instances, both the neural and the gonadal lesion may be determined by multiple effect of the same mutant gene. Sterility and small gonads associated with lesions of the central nervous system have been described in mice (40). This condition has been established as a spontaneous mutation and, genetically, it might be viewed as analogous to the so-called heredodegenerative diseases. In our case, available information does not allow more precise conclusions as to the genetic position of the two pathologic entities.

SUMMARY

Development of testicular atrophy and gynecomastia in a patient suffering from advanced multiple sclerosis is discussed in the light of the histologic and hormonal findings. It is suggested that hypogonadism in this case might have been caused by the interruption of a hypothetical pathway in the spinal cord, conducting stimuli to the gonads. Chromosomal sex, determined in the cells of both sides of the body, showed that the gynecomastia was not due to a female set of X-chromosomes, as would be expected according to the gynandromorphic intersex theory.

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FAMILIAL CONGENITAL MUSCULAR DYSTROPHY WITH GONADAL DYSGENESIS

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IN A family living in a small isolated village in Finnmark county, Norway, we have observed 7 persons suffering from congenital muscular dystrophy. Their symptoms were similar to those seen in congenital amyotonia (Oppenheim). Several children in the family had died very early in life; 3 others had been still born. In the third generation (III, Fig. 1) the child mortality was 33.3 per cent, whereas the average child mortality in Finnmark in the period 1926–1930 was 9.17 per cent. In the same generation, 2 siblings (Cases 1 and 2) were affected. In addition to the muscular dystrophy there was gonadal dysgenesis—ovarian agenesis and testicular

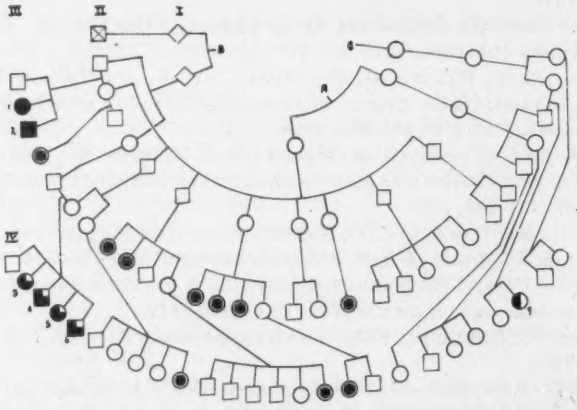

FIG. 1. *Family history.* Upright white squares and circles indicate normal men and women; slanted white squares indicate unknown sex. Black squares and circles indicate men with Klinefelter's syndrome and women with ovarian agenesis, both with cataract and muscular dystrophy. Black squares and circles with ¼ white area indicate men and women with muscular dystrophy, but without endocrine disorder. Black circle with ½ white area indicates woman with muscular dystrophy and epicanthus. Black double circles indicate stillbirths.

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insufficiency resembling Klinefelter's syndrome. Among the 26 persons in the fourth generation (IV, Fig. 1), 5 were affected (Cases 3, 4, 5, 6 and 7). In 1 of these, a girl aged 4 (Case 7), histologic examination demonstrated a slightly atrophic ovary, although the internal genitalia appeared normal on inspection. Later, bilateral cataracts developed in this child.

CASE REPORTS

Case 1

The patient was a woman aged 22 (Fig. 2). Her striated musculature had been underdeveloped since birth. She was unable to raise her head from the pillow until she was 1 year old, and could not stand up until she was 2 years old. The leg musculature was especially weak; she was inclined to fall and could hardly get up by herself. When she was 1 year old she suffered for some months from indigestion. As a child she was twice admitted to the hospital; the first time the diagnosis was Friedreich's ataxia, and the second time it was congenital muscular dystrophy. At 5 years of age she was operated

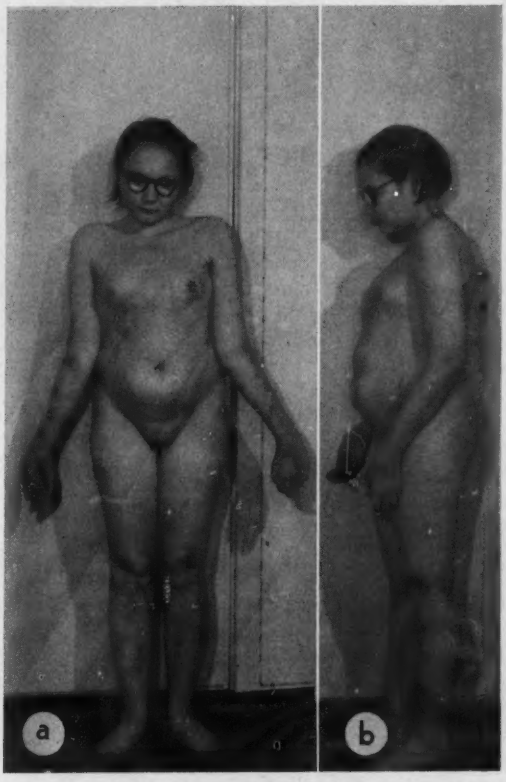

FIG. 2. *Case 1.* **a.** Showing cubitus valgus, elongated extremities and lack of pubic hair. **b.** Showing protruding abdomen, thoracic kyphosis and underdeveloped breasts.

upon for cataract. There had never been any convulsions or respiratory or pharyngeal disorders. She had never menstruated.

Physical examination. The patient seemed physically underdeveloped, although her IQ was normal. She walked with support, the movements being slow and guarded but not ataxic. The head was of normal shape and size, but the facial expression was dull. The shoulders were elevated. The extremities were long and the chest large in relation to the size of the body. Her weight was 44.5 Kg., height 139 cm., span 154 cm., upper measurement 68 cm., and lower measurement 73.5 cm. Thoracic kyphosis was marked. There was no muscular atrophy or pseudohypertrophy. Pubic hair was scant, and there

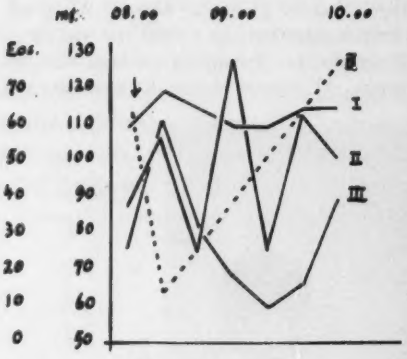

FIG. 3. Insulin tests (*Case 1*). Solid black lines indicate blood sugar values (mg./100 ml.) determined every twenty minutes. Dotted line indicates the eosinophil count per cu. mm. of blood.

FIG. 4. *Case 1.* Thin, fibrous ovaries found at laparotomy.

was no axillary hair. The breasts were underdeveloped and the nipples widely separated. The thyroid gland was small. The skin was normal. Upon rectal exploration, the uterus seemed infantile.

Neurologic examination. Vision was more reduced than would be expected following a cataract operation. There was slight ptosis and a convergent strabismus. No involuntary movements or muscular twitchings were observed. Movements were free in all joints and the metacarpophalangeal, hip, tarsometatarsal and metatarsophalangeal joints were hyperflexible. The musculature was hypotonic without signs of spasticity, rigidity or myotonia. With the exception of the masticatory and respiratory musculature, there was marked, symmetrical lack of strength in all striated muscles. The deep reflexes were normal.

Roentgenologic examination. The sella turcica was normal. Ossification of the distal arm and leg bones was delayed. There was bilateral cubitus valgus (25 degrees). The

corpus on the fourth metatarsal bone was shortened on both sides. All bones were slender, and manifested a slight degree of osteoporosis.

Laboratory examination. The spinal fluid was normal. Blood levels of sugar and electrolytes, and the blood count, were also normal. Urinary creatine was 197.5 mg. per day. In the insulin test, 3 blood sugar curves showed an increase from normal values by 10 mg., 20 mg. and 35 mg. per 100 ml., respectively during the first twenty minutes

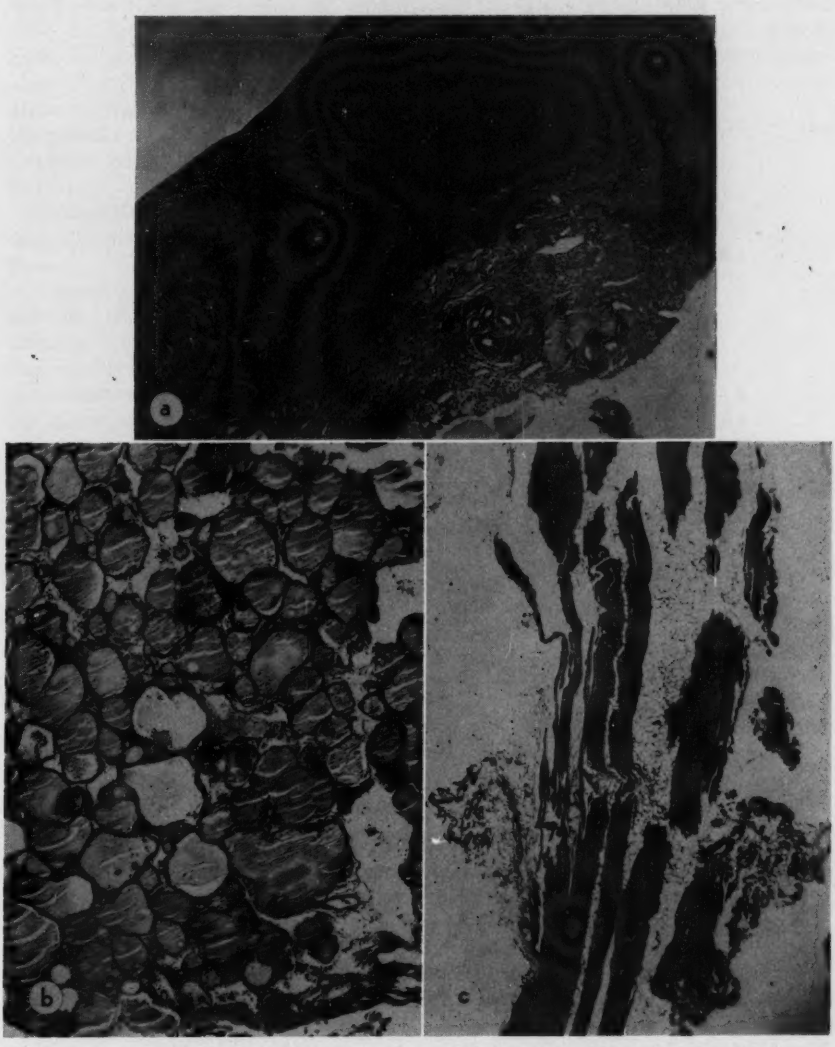

FIG. 5. *Case 1.* **a.** Section from ovary. **b.** Section from thyroid gland. **c.** Section from striated musculature.

(Fig. 3). The urinary excretion of gonadotropic hormones was increased (more than 40 mouse units) in 3 of 4 determinations. The average fluid intake per day was 800 ml. With Kepler's test the diuresis was 750 ml., indicating fair renal function. Results of a Thorn test (25 mg. of corticotropin intramuscularly and 0.3 mg. of adrenaline subcutaneously on each of two days) showed a decrease in the number of eosinophils by 30

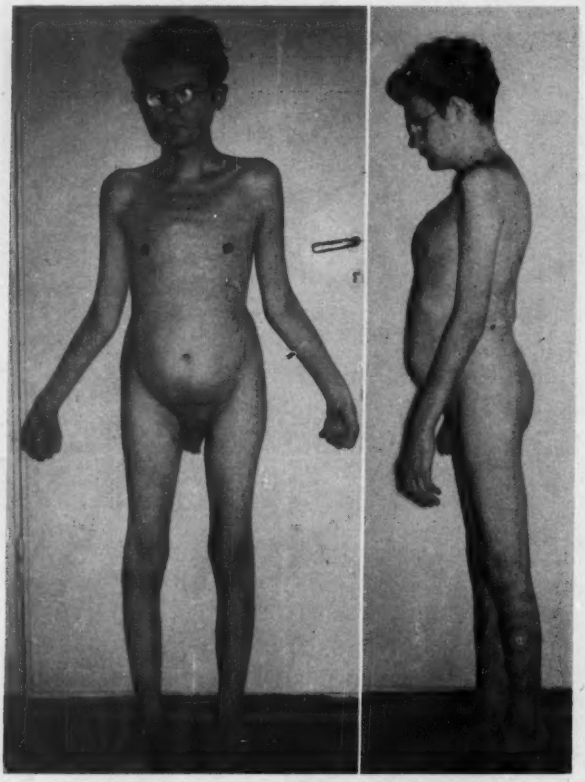

FIG. 6. *Case 2.* Front and side views—brother of the patient in Figure 2.

and 40 per cent, respectively. Urinary neutral 17-ketosteroids were normal. The urinary estrogenic titer was less than 18 mouse units per day. The basal metabolism was −32 per cent. The serum cholesterol level was 135 mg. per 100 ml.

Surgical and histologic findings. There were clinical signs of muscular dystrophy and ovarian agenesis, confirmed by the laboratory findings. In order to provide further support to the diagnosis, *exploratory laparotomy* was performed. The internal genitalia were infantile, the corpus uteri being the size of an almond and of smooth consistency. The white, fibrous ovaries were pencil-shaped, measuring 30 mm.×3–4 mm. (Fig. 4). The *histologic examination* showed fibrous ovarian tissue without signs of primary follicles; a few cicatricial follicles were seen (Fig. 5a). A section from the thyroid gland (Fig. 5b) showed regular follicles filled with colloid substance, and no signs of vacuoli-

zation. The epithelium was low and the nuclei rather small. A section of the musculature (Fig. 5c) showed irregular bundles of striated muscle fibers separated by a large amount of fatty tissue. The fibers were of normal size.

Case 2

This 26-year-old man (Fig. 6), like the first patient, was unable to stand up until he was 2 years of age, had a period of indigestion, and was operated upon for cataract as a child. Except for the sex difference, on the whole he demonstrated symptoms similar to those in Case 1. His weight was 40.5 Kg., height 158 cm., span 158 cm., upper measurement 72 cm. and lower measurement 75 cm. The external genitalia appeared normal. However, the testes were infantile and soft, the prostate was smaller than normal, and the scant pubic hair was of feminine distribution.

Neurologic and roentgenologic examination. The findings were similar to those in Case 1.

Laboratory examination. During the insulin test (Fig. 7), in the course of twenty minutes, 2 out of 3 curves showed blood sugar levels which were slightly increased above normal. At the same time the number of eosinophils decreased by 88 and 23 per cent, respectively. The third curve showed decreased blood sugar values while the number of eosinophils increased by 38 per cent. Fluid intake and diuresis were 845 ml. and 670 ml., respectively. With the Thorn test there was a 52 per cent decrease in the number of eosinophils. In 3 assays, no increase in urinary gonadotropins was found. The mean average excretion of urinary neutral 17-ketosteroids was 3.1 mg. per day. Urinary estrogens were increased. The basal metabolic rate was +5 per cent. The serum cholesterol level was 160 mg. per 100 ml.

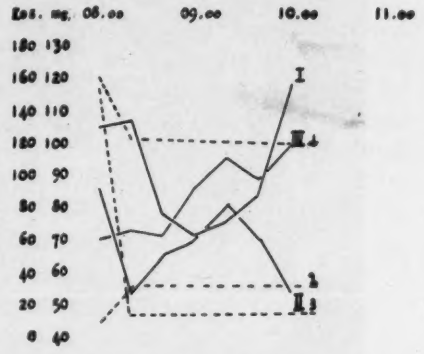

FIG. 7. Insulin tests (*Case 2*). (For key, *see* legend to Figure 3.)

Histologic findings. Histologic examination of the testis (Fig. 8) showed a thick, fibrous capsule and scanty testicular canals with few Sertoli cells. In the vascular stroma there were large aggregations of Leydig cells. Most of the section, however, consisted merely of a hyaline substance.

DISCUSSION

Clinically the first patient presented the picture of ovarian agenesis (gonadal dysgenesis). The diagnosis was confirmed by the increased excretion of urinary gonadotropic hormones, and the findings on inspection of the internal genitalia and histologic examination of the ovary. No previous description of muscular dystrophy associated with specific gonadal dysgenesis has been found in the literature available.

In 3 insulin tests the blood sugar level rose; at the same time the number of eosinophils decreased by 80 per cent. A possible explanation may be that the increase in urinary gonadotropins was associated with an

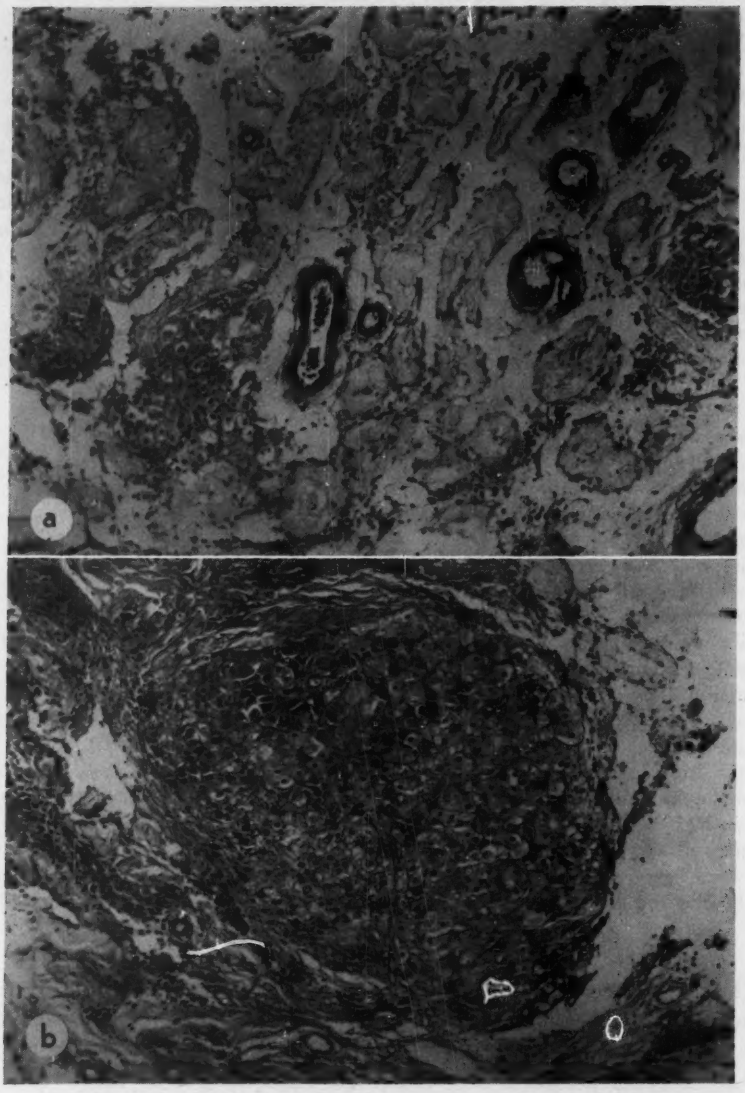

FIG. 8. *Case* 2. **a.** Section from testis showing preponderance of hyaline substance. **b.** High-power view of an aggregation of Leydig cells.

increased vascularization of the hypophysis, resulting in a potential hyperfunction and increased insulin resistance.

The second patient presented testicular insufficiency associated with symptoms similar to those in Case 1. Histologic examination of the testis showed large aggregations of Leydig cells, as usually seen in Klinefelter's syndrome. The excretion of gonadotropic hormones was not increased and the basal metabolism was normal. Urinary neutral 17-ketosteroids were reduced, possibly due to decreased testicular production of androgens. Clinically, there were certain signs of femininization, and the excretion of estrogens was increased.

Thus, in 2 siblings, a familial congenital disease has been described, characterized by muscular dystrophy and gonadal dysgenesis. The disease developed shortly after birth and was found also in 5 other members of the same family. The course was stationary, with a tendency towards remission. In the cases with cataract, the diagnosis of congenital amyotonia cannot be excluded. In many respects the syndrome resembled Oppenheim's disease, which may be familial; cataract is, however, not considered to be a symptom. That gonadal dysgenesis itself may be familial is suggested by the occurrence of the described hypogonadal disorders in 2 siblings.

SUMMARY

A report is presented of a sister and brother, one with ovarian agenesis and the other with hypogonadism resembling Klinefelter's syndrome, who suffered from dystrophia musculorum congenita (amyotonia congenita, Oppenheim's disease) and infantile cataract. In the family there were 5 other children with the same muscular disorder; all of them had infantile cataract. In 1, a 4-year-old girl, slight atrophy of the ovaries was found upon histologic examination.

LAURENCE-MOON-BIEDL SYNDROME IN AN ARAB BOY: FAMILIAL INCIDENCE

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DURING the past eighty-nine years, following the report of 4 cases by Laurence and Moon (1) from the Royal Eye Hospital in London, some 300 cases of the Laurence-Moon-Biedl syndrome have been described in the medical literature (2). Of these, however, only 20 to 30 per cent have exhibited the complete picture of the syndrome comprising the six cardinal features of obesity, retinitis pigmentosa, polydactylism, mental retardation, hypogonadism and familial incidence (3). The reported patients have been of many different races—Negroes, Indians, Greeks, Jews, Bantus, Caucasians and Anglo-Saxons. The present case seems worth recording, not only because it has all the major features of the syndrome but also because, to the author's knowledge, it is the first report of this condition in an Arab.

CASE REPORT

The patient was a 13-year-old Arab from the village of Idna in the Hebron District (Fig. 1). He offered no complaints, but his father stated that he thought the boy was mentally retarded and suffered from night blindness.

On examination the boy looked cheerful. Intelligence could not be accurately graded because of the lack of psychiatric aid, but it was easy to recognize a mental deficiency. He was obese, mostly around the chest anteriorly, and of short stature. He weighed 50.4 kilos (average for his age, 41.7) and was 139 cm. tall (average, 152 cm.). There was no hair on the face, or in the axillary and pelvic regions. The face was rounded (moon shaped). He had 6 fingers on each hand and 6 toes on each foot (Fig. 1). The hands were flat and spade-like. The testes were small and the penis was infantile. His blood pressure was 110/70. Otherwise no abnormality could be detected in the cardiovascular, respiratory, gastro-intestinal and urinary systems. No neurologic abnormalities were found. The eyes were examined by Dr. Norman Manson, Consultant, who gave the following report: "V.R. 6/60, V.L. 6/36. Defective vision is partly due to myopic astigmatism of about 2 diopters and can be corrected to 6/18, 6/18. Pupils react normally. Both fundi show incomplete retinitis pigmentosa, *i.e.*, there is great attenuation of vessels especially arterioles without the migration of pigment along the vessels seen in typical retinitis pigmentosa. There is in this case a very thin layer of pigment allowing the choroidal vessels to be seen. These are sclerosed and show up as yellow streaks. There is also a solitary mass of pigment in the upper nasal quadrant of each retina."

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* Assistant Physician.

FIGURE 1

X-ray examination of skull did not reveal any abnormalities. The sella turcica was normal in size and shape. Serologic tests of the blood yielded negative results. Blood biochemical values were within normal limits. Urinary 17-ketosteroid excretion was not studied.

DISCUSSION

It is generally agreed that the Laurence-Moon-Biedl syndrome is a manifestation of a hereditary condition with recessive transmission (4, 5). The complexity of the syndrome is probably the result of various mechanical, endocrine, and other modifying factors superimposed on the less complex basic genetic formula. The incidence of this disorder in the family of the boy presented here may be seen in Figure 2.

The 2 afflicted members of the first generation died in middle age of unknown cause. According to eye-witness accounts, they had all the characteristics of the syndrome. Inquiry and inspection did not reveal polydactylism or any associated gross anomalies in the other members of the family.

The presence of consanguinity is apparent. Burn has shown that there is a high incidence of consanguinity in the families of reported cases (6).

The features of mental deficiency, polydactylism and retinitis pigmentosa are supposed to be a direct manifestation of a defective germ plasm, whereas the hypogenitalism and obesity are thought to be secondary results of pituitary and hypothalamic hypoplasia (7). Russell Brain in his textbook includes the description of this condition under "Syndromes of the

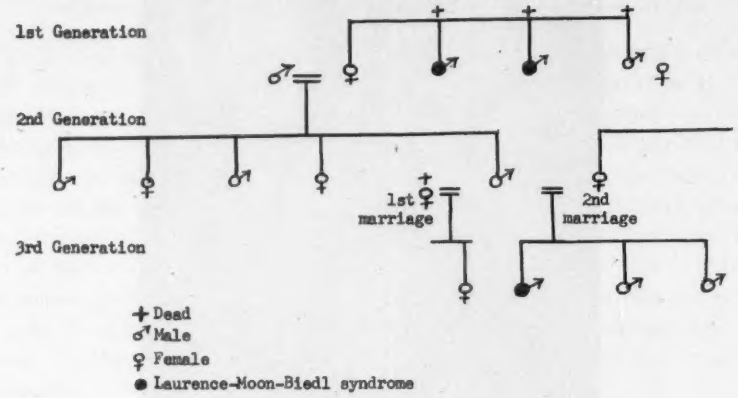

FIGURE 2

hypothalamus "(8). Only a few autopsies have been performed in these cases, so there are not enough pathologic data to support the foregoing hypothesis. Over fifty concomitant anomalies have been reported, but their presence does not seem to be essential for the diagnosis of the syndrome.

The diagnosis of the Laurence-Moon-Biedl syndrome in its full picture is easy and straightforward. It has to be differentiated from other causes of juvenile adiposity. The present case had been previously diagnosed as Fröhlich's syndrome. Encephalitis lethargica, idiopathic adiposogenital dystrophy, internal hydrocephalus, and tumors of the pituitary region have to be considered (8). The retinitis pigmentosa may at times be atypical. Macular dystrophy is also found, either alone or associated with atypical retinitis pigmentosa. Polydactylism may not be apparent on inspection, as sometimes the supernumerary digits are represented by buds which are visible only by x-ray examination.

Almost all the drugs in the armamentarium of the endocrinologist (including adrenocorticotropin) have been tried in the treatment of this condition. It is not surprising that none has been effective.

SUMMARY

The Laurence-Moon-Biedl syndrome in its complete picture is described as occurring in an Arab boy. The family history is presented. The various features of the syndrome are briefly reviewed.

Acknowledgment

I am grateful to Dr. Vahan H. Kalbian, Chief, Department of Medicine, for allowing me to report this case.

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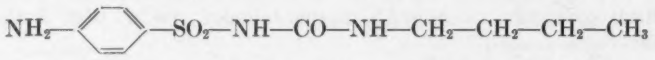
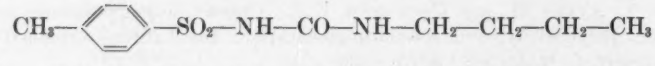
Editorial

THE ARYLSULFONYLUREAS AND DIABETES MELLITUS

RECENTLY a great deal of interest has been aroused by reports of two remarkable compounds which can induce a lowering of the blood sugar level when taken by mouth. These substances have the following names and structural formulae:



BZ 55 Carbutamide N-*p*-amino-benzolsulfonyl-N′-butylurea



D 860 Tolbutamide N-4-methyl-benzolsulfonyl-N′-butylurea (Orinase)

Carbutamide, which is a sulfonamide, was originally tested for antibacterial action. In some of the subjects receiving it, symptoms suggestive of hypoglycemia developed and a lowered concentration of blood sugar was demonstrated. In retrospect, this phenomen should not have been unforeseen, because as early as 1942 depression of the blood sugar level following administration of a sulfonamide had been reported, although the mechanisms involved were not further investigated.

Carbutamide and tolbutamide appear to have essentially the same actions. Carbutamide is weakly antibacterial and also slightly goitrogenic in rats when given in large amounts. The latter action appears essentially negligible in humans. Both compounds cause a lowering of the blood sugar level in healthy animals and humans and in certain patients with diabetes mellitus.

The mechanisms involved in the hypoglycemic effect appear to be complex. The presence of insulin is essential. For example, neither carbutamide nor tolbutamide has a hypoglycemic effect in alloxan-diabetic rats, depancreatized dogs and human subjects. An immediate release of stored pancreatic insulin by the arylsulfonylureas is suggested by the occurrence in normal subjects of a rapid decrease in the concentration of blood sugar in a manner similar to that observed following the intravenous injection of insulin. In certain diabetic subjects in whom there is some insulin produc-

tion (but probably less than normal), a gradual decline in the blood sugar level occurs. This finding, as well as studies *in vivo* and *in vitro*, has led to the impression that another mode of action is through modification of the rate of inactivation of insulin. The arylsulfonylureas appear to act as noncompetitive inhibitors of hepatic insulinase. A third mechanism, decreased gluconeogenesis, is suggested by the absence of the usual rise in the concentration of blood sugar after administration of fructose in subjects who have received arylsulfonylureas. There is considerable evidence that no alteration in the peripheral effects of insulin nor in the rate of secretion of glucagon, epinephrine, adrenocortical steroids or anterior pituitary tropic hormones is induced by the arylsulfonylureas.

The obvious corollary of the demonstration of sulfonamide-induced hypoglycemia was the utilization of these agents in the treatment of diabetes mellitus. Clinical studies in Germany and the United States have now been sufficiently extensive to permit tentative conclusions about the role of the arylsulfonylureas in therapy of this disease (1–4). Treatment is most likely to be successful in elderly or middle-aged diabetics in whom ketosis does not readily develop when insulin is withheld. In suitable patients these drugs have a dramatic and gratifying effect. Within a short time after administration of an appropriate oral or intravenous dose, the blood sugar level is in or near the normal range. Continued oral administration usually results in maintenance of the fasting blood sugar level within the range which would be achieved with insulin therapy.

The arylsulfonylureas do not appear to be effective in the more severe type of diabetes such as that found in children or in some adults who readily become ketotic upon withdrawal of insulin. These drugs have no value as a substitute for insulin in the treatment of acidosis or coma. They may be of value in some patients whose insulin requirements vary widely, by permitting a more easy regulation of the insulin dosage.

The incidence of toxic reactions following administration of these substances is low. A few instances of dermatitis and of leukopenia have been reported. As yet, no serious morbidity has been proved to be the result of the administration of these agents. Several deaths have occurred in association with carbutamide therapy, but no causal relationship has been clearly demonstrated. More reactions have been reported during carbutamide therapy than during treatment with tolbutamide. Experience with these substances must be greatly increased before definite conclusions concerning their safety can be reached.

Although the final chapter on toxic reactions is still to be written, other dangers in the use of the arylsulfonylureas have already become obvious. These hazards do not lie in the risk of untoward reactions to the medication, but rather are the indirect result of the very success of treatment. The best

therapeutic responses are obtained in patients who, in many instances, are perhaps least suited psychologically to such a simple and easy method of treatment—namely, those in whom diabetes is aggravated by obesity and in whom improvement or even disappearance of diabetes would be expected following weight reduction. Successful treatment with arylsulfonylureas eliminates the persistent reminder of the necessity for weight loss provided by the daily encounter with the insulin syringe, and obesity may actually increase because of the utilization of calories which would otherwise be wasted as glycosuria. Successful treatment of mild diabetes mellitus with the arylsulfonylureas may, then, augment the hazards due to obesity, whereas treatment by means of weight loss may decrease the hazards of both obesity and diabetes. The ease of treatment with these new drugs may also result in carelessness in the observance of dietary measures, even in patients in whom weight loss is not necessary.

Until a great deal more experience has accumulated, it would seem justified to assume an attitude of guarded optimism not only with regard to the clinical usefulness of these compounds but also with regard to the depth of insight into physiologic mechanisms which they may afford. Tempering our enthusiasm should be the awareness that, as has so frequently happened, a potent therapeutic agent which initially appears to possess little toxicity may ultimately turn out to be a sensitizing agent of awesome power. Certainly a previous history of sensitization to a sulfonamide should warn the physician who prescribes these compounds to be especially alert concerning reactions.

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Letters to the Editor

BIOSYNTHESIS OF ANDROGENS FROM PROGESTERONE BY HUMAN TESTICULAR TISSUE *IN VITRO**

To the Editor:

The conversion, by rat testicular tissue preparations, of 4-C^{14}- and 21-C^{14}-labelled progesterone to the two androgens 4-androstene-3,17-dione and testosterone has recently been reported (1) as proceeding via 17α-hydroxyprogesterone and cleavage of the side-chain (1, 2). These studies reveal the important role of progesterone and its derivative, 17α-hydroxyprogesterone, in the steroidogenetic pathway to androgens in the rat testis. We wish to report a similar conversion of 4-C^{14}-progesterone by *human* neoplastic testicular tissue, to radioactive 17α-hydroxprogesterone, 4-androstene-3,17-dione and testosterone. The detailed experimental data will be published elsewhere.[1]

Nine-tenths of a gram of tissue slices from a virilizing human testicular tumor[2] was incubated in human serum with added gonadotropins, glucose, fumarate and 4-C^{14}-progesterone (2 mg., 175,000 counts/minute/mg.) for three hours. Immediately prior to extraction, crystalline steroids were added to the incubation flask as diluents of the anticipated radioactive conversion products. The process of extraction and fractionation of the lipids was carried out as previously described (3). The individual carrier steroids were isolated by means of paper chromatography, and were then subjected to stringent testing for radiochemical purity. The following radioactive steroids were obtained: a) 17α-hydroxyprogesterone, 1200 c/m/mg., the specific activity remaining unchanged through several recrystallizations,

* This investigation was supported in part by a research grant made by the Charles A. King Trust of Boston, Massachusetts.

[1] This study is a part of a more extensive investigation, being made jointly by our two laboratories, of the biochemical aspects of steroid production by this tumor; portions of the study have been briefly reported (3, 4).

[2] The patient was a boy aged 5 years and 7 months. The diagnosis, based on pathologic findings, was interstitial-cell tumor of the testis; crystalloids of Reinke were present. The fresh tissue was made available to us by Doctors L. M. Lister and Frank L. Engel of Duke University, Durham, N. C., whose interest and cooperation we gratefully acknowledge.

conversion to the dioxime and crystallization to constant melting-point; b) 4-androstene-3,17-dione, 319 c/m/mg., the specific activity remaining constant through several crystallizations, formation of the oxime and chromatography on paper followed by crystallization; and c) testosterone isolated as the acetate, 107 c/m/mg., the specific activity remaining unchanged on saponification, crystallization followed by conversion to the oxime, chromatography on paper and recrystallization. Several other steroids, such as 11β-hydroxyprogesterone and 11-ketoprogesterone which were added as carriers to this incubation, were recovered essentially devoid of radioactivity.

In addition to the foregoing, conversion of 4-C^{14}-progesterone to radioactive 17α-hydroxyprogesterone, 4-androstene-3,17-dione and testosterone was achieved with a brei prepared from normal adult rat testes.

In view of these recent findings, it appears that the pathway, progesterone $\rightarrow$17α-hydroxyprogesterone$\rightarrow$4-androstene-3,17-dione$\rightarrow$testosterone (1, 5), is an important route in the biosynthesis of androgens of testicular origin.

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts

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RALPH I. DORFMAN, PH.D.

August 1, 1956

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Acknowledgment

The competent assistance of Mr. Basil Dmuchovsky in this work is acknowledged.

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ANTICORTISOL ACTION OF 2-METHYL-9(α)-CHLOROCORTISOL

TO THE EDITOR:

It had recently been shown that 2-methyl-9(α)-fluorocortisol (Me-F-COL) is highly effective in antagonizing the antiphlogistic, catabolic, thymolytic and splenic atrophy-producing actions of cortisol acetate (COL-Ac) in the adrenalectomized rat (1). In general, 9(α)-chloro substitution is even more effective than 9(α)-fluoro substitution in increasing the mineralocorticoid effects of cortisone and cortisol derivatives. Hence it seemed of interest to explore the possible anticortisol actions of 2-methyl-9(α)-chlorocortisone. This compound has kindly been made available for us—in the form of its acetate (Me-Cl-COL-Ac)—by The Upjohn Company.

MATERIALS AND METHODS

Ninety-five Sprague-Dawley rats, with an average initial body-weight of 160 Gm. (range, 155–166 Gm.), were bilaterally adrenalectomized and subdivided into five groups, as indicated in Table 1. Throughout the observation period these rats were maintained exclusively on "Purina Fox Chow" and tap water, without special salt supplements. Hormone treatment was initiated immediately after adrenalectomy. The daily doses

TABLE 1. ANTICORTISOL ACTION OF 2-METHYL-9(α)-CHLOROCORTISOL

Group	No. of rats	Daily dosage of mineralocorticoid	Final body-wt. (Gm.)	Wt. gain (%)	Amt. of exudate in g. pouch (ml.)	Wt. of thymus (mg.)	Wt. of spleen (mg.)
I	20	None	154±2.1	−4	12±0.88	161±10.5	520±17.3
II	20	Me-Cl-COL-Ac, 5 μg.	172±1.7	+7	19±1.2	202±10.5	710±34.5
III	20	Me-Cl-COL-Ac, 50 μg.	166±1.8	+3	21±0.99	175±10.1	656±26.0
IV	10	Me-Cl-COL-Ac, 100 μg.	161±2.5	+1	19±1.1	105±10.4	584±18.4
V	25	DOC-Ac, 100 μg.	169±1.6	+6	20±1.2	202± 9.9	653±26.4

were as follows: cortisol acetate, 400 micrograms (μg.) (Groups I–IV); Me-Cl-COL-Ac, 5 μg. (Group II), 50 μg. (Group III) and 100 μg. (Group IV); and desoxycorticosterone acetate (DOC-Ac), 100 μg. (Group V). The latter substance, which like aldosterone is an anticortisol compound of known activity (2), served merely as a control. All steroids were administered subcutaneously as microcrystals, the daily dose being contained in 0.2 ml. of aqueous suspension medium.

As in our previous observations on aldosterone and Me-F-COL, the granuloma-pouch technique (3) was used for the quantitative assessment of inflammation. Forty-eight

hours after the initiation of hormone treatment, pouches were prepared by the injection of 25 ml. of air under the dorsal skin, this being immediately followed by the injection of 1.0 ml. of 1 per cent croton oil (in corn oil) into the air-space so created. All animals were killed on the thirteenth day after adrenalectomy. At this time the exudate was measured in milliliters, by aspiration into a graduated syringe, and the thymus and spleen were weighed after fixation in Susa solution. One animal in each of Groups II and V, as well as 2 animals of Group III had to be eliminated because of accessory adrenal rests.

RESULTS

It is evident from Table 1 that, under these conditions, even as little as 5 μg. of Me-Cl-COL-Ac was approximately as effective as 100 μg. of DOC-Ac in significantly inhibiting the loss of body-weight, the suppression of exudate formation and the involution of the spleen which occur under the influence of COL-Ac alone. Interestingly, higher doses of Me-Cl-COL-Ac proved to be less effective in this respect and the highest dose employed in these series (100 μg.) actually enhanced the thymus involution normally induced by COL-Ac alone.

DISCUSSION

The decrease in anticortisol effect noted with increasing doses of Me-Cl-COL-Ac is paradoxical at first sight, but it should be kept in mind that in our earlier work with the corresponding fluorinated cortisol derivative we had observed the same type of dose: effect relationship. This is in agreement with the "law of intersecting dose-effect curves." It had been noted that, when a solution containing fixed proportions of COL-Ac and DOC-Ac was administered to adrenalectomized rats, the cortisol action (catabolism, inhibition of exudation, thymolysis and splenic atrophy) predominated at high levels of dosage, but the opposite, desoxycorticosterone-type of activity predominated at low dosage levels. This was ascribed to the fact that DOC-Ac activity rises rapidly to its optimum level, but then a "ceiling" is reached and raising the dose further will not increase the effect. Cortisol-type activity, on the other hand, rises more slowly and does not flatten out until it far exceeds the "ceiling" of its antagonist (4). It would therefore appear that—like the corresponding fluorinated compound—Me-Cl-COL-Ac possesses some glucocorticoid (antiphlogistic) activity, though in proportion to its very high mineralocorticoid (prophlogistic) action, this contaminating effect is extremely slight. We did not test dosages of Me-Cl-COL-Ac below the level of 5 μg. per day; hence we cannot state with certainty that the anticortisol effect of this compound is only twenty times that of DOC-Ac. However, it is evident by comparison with our earlier findings on aldosterone (2) and Me-F-COL (4), that the action of Me-Cl-COL-Ac at least equals, and probably exceeds, the anticortisol action of the most potent mineralocorticoids so far examined. This view is

further supported by another series of experiments (5) in which we have shown that Me-Cl-COL-Ac is about four hundred times as active as DOC-Ac in producing nephrosclerosis and cardiovascular hyalinosis in suitably conditioned rats.

SUMMARY

In adrenalectomized rats bearing a "granuloma pouch" it has been demonstrated that 5 μg. per day of 2-methyl-9(α)-chlorocortisol acetate (Me-Cl-COL-Ac) antagonizes the catabolic, antiphlogistic, thymolytic and splenic atrophy-producing actions of 400 μg. per day of cortisol acetate (COL-Ac). Higher dosages of Me-Cl-COL-Ac are less effective in these respects. In view of the "law of intersecting dose-effect curves," this apparent paradox in the dose:effect relationship suggests that Me-Cl-COL-Ac is highly effective as a mineralocorticoid but possesses a comparatively slight, though definite, glucocorticoid activity as well.

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The authors gratefully acknowledge generous supplies of "Cortril" (COL-Ac) from the Pfizer Laboratories; of 2-methyl-9(α)-chlorocortisol from The Upjohn Company; and of "Cortate" (DOC-Ac) from Schering Corporation.

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The Endocrine Society

THE 1957 ANNUAL MEETING

The Thirty-ninth Annual Meeting of The Endocrine Society will be held in the Hotel New Yorker, New York City, Thursday, Friday and Saturday, *May 30 and 31, and June 1, 1957.*

The Committee on Local Arrangements is Dr. Rulon W. Rawson as Chairman with Drs. Earl T. Engle, Joseph W. Jailer, Warren O. Nelson, and Martin Sonenberg as members of the Committee.

All Scientific Sessions will be held in the Hotel New Yorker. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, May 31, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately inasmuch as the hotels expect to be filled to capacity. Make reservations directly with the New Yorker, advising time of arrival and departure date. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be strictly limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Eleanor Venning, Royal Victoria Hospital, Montreal, Quebec, Canada, *not later than February 1, 1957. It is imperative that the abstracts be informative and complete with results and conclusions—not a statement that these will be presented at the meeting*—in order that they may be of reference value and suitable for printing in the program and journals of the Society. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. Reference, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*,

who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter perfect, since there will be no opportunity for proof reading by authors.

THE 1957 AWARDS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada. Dr. Carl R. Moore was the recipient in 1955 and Dr. Frederick L. Hisaw in 1956.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg; 1955—Dr. Jack Gross; 1956—Dr. Alfred M. Bongiovanni. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST AND THE SQUIBB FELLOWSHIPS

The Ayerst Fellowship was established in 1947 and the Squibb Fellowship in 1956. They are designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. Each Fellowship is awarded on alternate years and the stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of the Endocrine Society; the Ciba Award; and the Ayerst and the Squibb Fellowships may be made by any member of The Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *November 1* each year.

Proposals for appointments as Scholars of The Endocrine Society should

be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *November 1* each year.

The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1.

The American Goiter Association

THE 1957 ANNUAL MEETING

The next Annual Meeting of The American Goiter Association will be held in the Statler Hotel, New York City, on *May 28, 29 and 30, 1957.*

THE VAN METER PRIZE AWARD FOR 1957

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in the Hotel Statler, New York, May 28, 29 and 30, 1957, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, *not later than January 15, 1957.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

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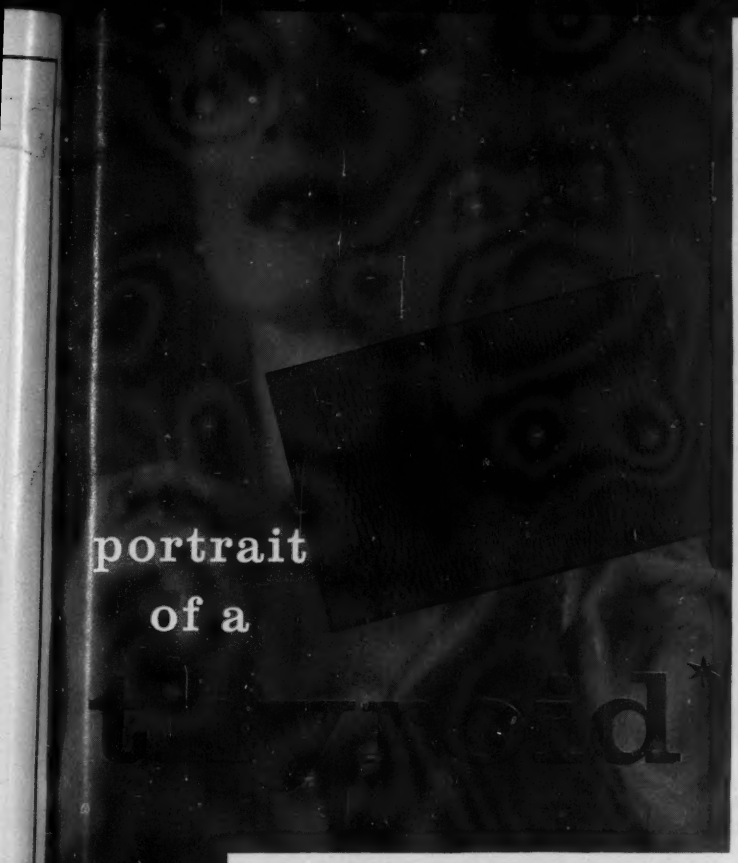

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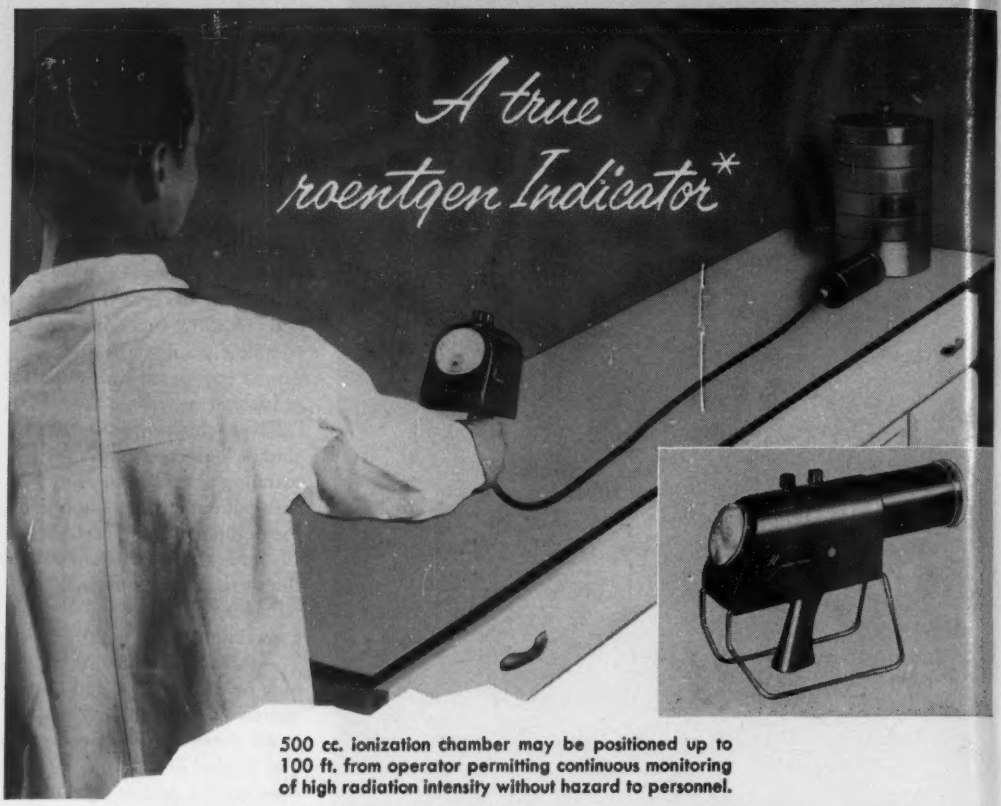

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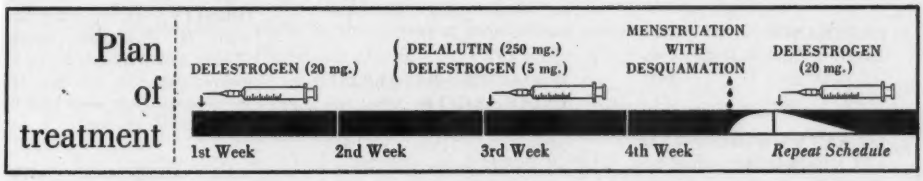

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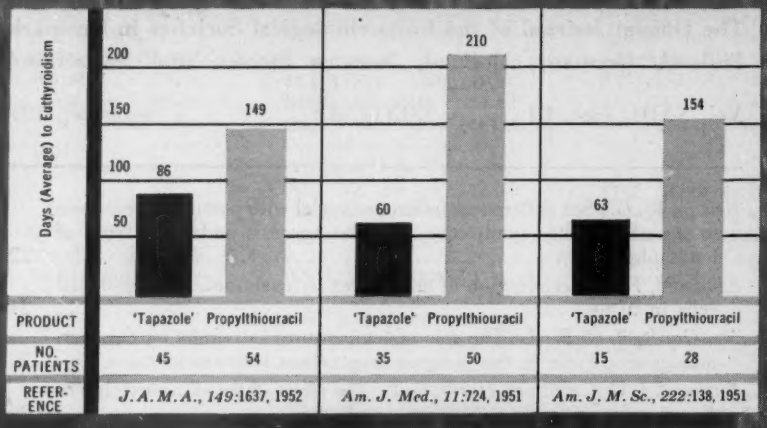

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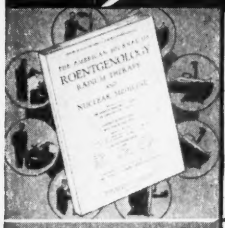

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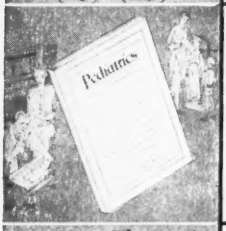

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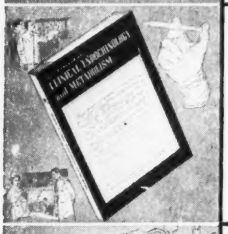

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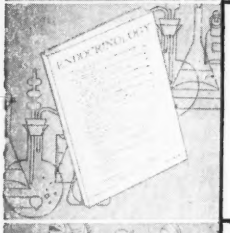

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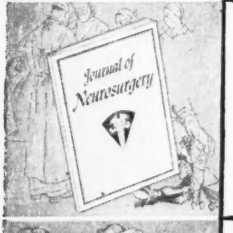

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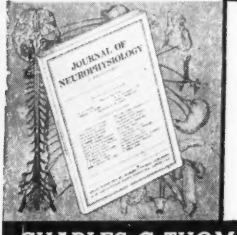

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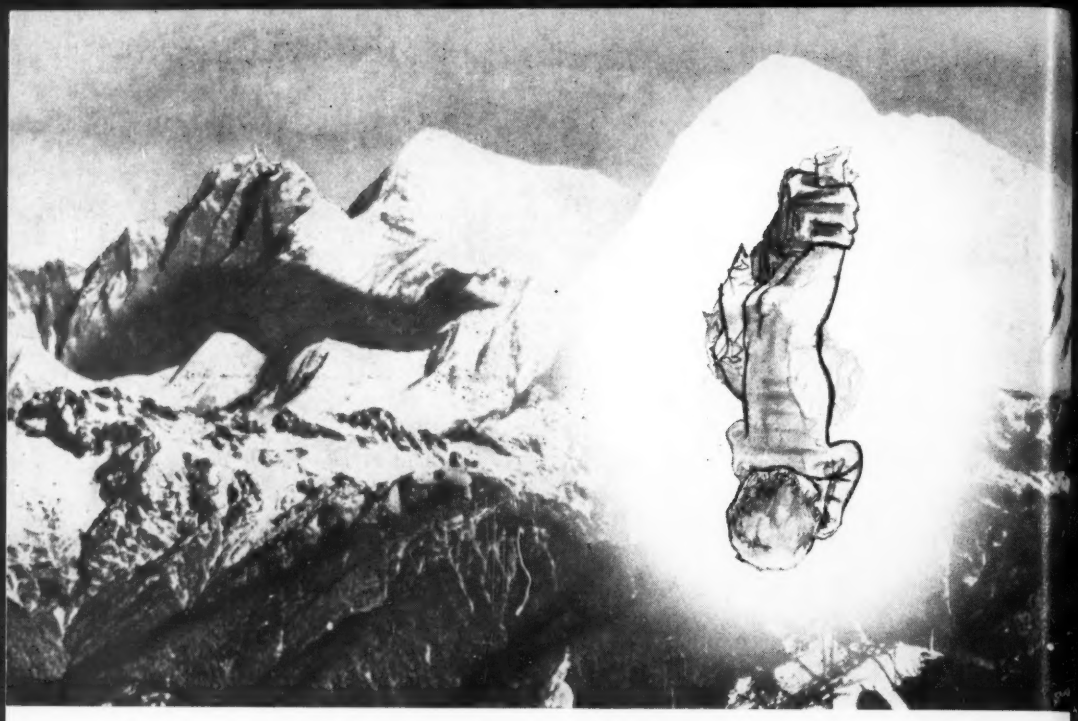

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